New annelation methods for nitrogen heterocycles

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NEW ANNELATION METHODS FOR NITROGEN HETEROCYCLES

Submitted by

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CONTENTS

CHAPTER ONE

CHAPTER TWO

The use of α,β-aminoalcohols as intermediates for the synthesis of aziridines

CHAPTER THREE

Synthesis of the aziridines

CHAPTER FOUR

Alternative approach to ergot alkaloids

SUMMARY

The thesis is organised into two sections, the first dealing with an investigation of a new approach to the anti-emetic drug levonantradol. In this work the chemical and photochemical cyclisation reactions of imines, e.g.(1a), were analysed in an attempt to generate the heterocyclic ring of the drug.

This study was beset by the instability of the intermediates and ultimately it was abandoned in favour of a related programme designed to investigate new routes to ergotamine types.

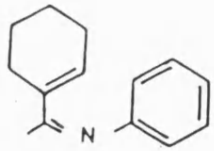
Thus the second part of this thesis describes a number of attempts to generate tetrahydronaphthyl-aziridines which might afford the ergotamine system by a novel ring expansion. In the early attempts two new isomeric spiro β- lactams (2a and 2b) were obtained during the photo-reaction of ethyl diazoacetate and the N-phenyltetrahydronaphthyl-α-imine (3a).

Other carbenes were also investigated for the (1,2) - cycloaddition to the imine. However, instead of obtaining the expected three-membered aziridine unit, an interesting addition to - C_2 of the tetrahydronaphthalene ring resulted giving another new compound (4a). An unexpected dimer (5a) was obtained in the reaction of the same imine with dimethylsulphonium methyl ylide during which an oxidation step was involved.

Chapter two of the second part explains a different approach to the formation of aziridine. The known 1-hydroxyl-1- (aminomethyl) - tetrahydronaphthalene (6a) was N-protected and reacted with triphenylphosphine - carbon tetrachloride to produce the new compound (7a) instead of the aziridine. Using the same aminoalcohol the two unknown spiroxazolidinones (8a and 8b) were prepared. It was anticipated that these compounds could extrude carbon dioxide on heating to give the aziridines, but was not realized.

In the third chapter of this part a successful route is described during which the desired spiroaziridine (9a) was obtained. However, this new aziridine has proved to be rather unstable if not N-protected.

The fourth chapter made use of yet another possibility to the ergot system. The compound (10a) was used to examine this possibility and during which some interesting aspects about this compound were observed.



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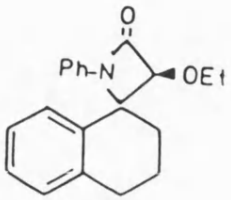

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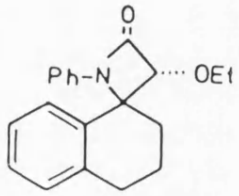

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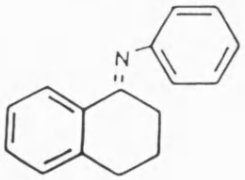
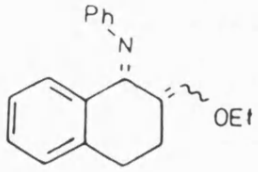


(3a)



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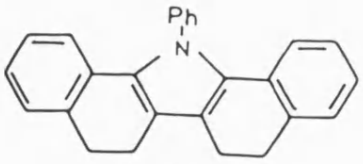

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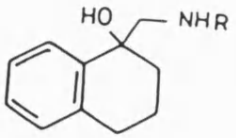
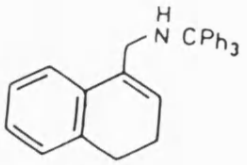


(6a)



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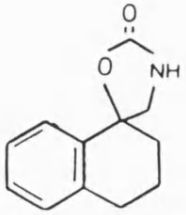
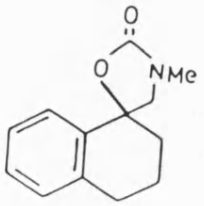


(8a)



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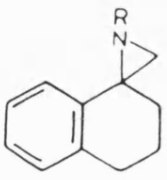
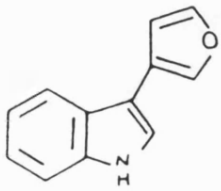


(9a)



(10a)

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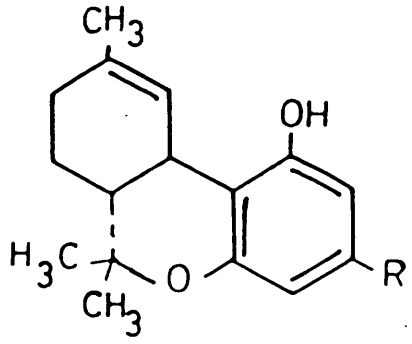
THE CANNABINOID RELATED HETEROCYCLES

1.1 INTRODUCTION

1.1.1 A general view of cannabinoids

The misuse of marijuana[1], which started in a substantial way in the early 1960's, is still on the increase. By 1975 over 36 million Americans had tried the drug, and among the 20–24 age group over 10% were using it on a daily basis. This has caused serious concern to society and marijuana has become the subject of intense sociopolitical conflict. On the other hand, the recent use of marijuana and its active constituent (-)-Δ^1-3,4-*trans*-tetrahydrocannabinol(Δ^1-THC) in treating glaucoma and as an antinauseant in patients undergoing cancer chemotherapy has gained public attention. In other countries, particularly China, India and the Middle East, the therapeutic value of cannabis has been well documented for centuries, and folklore medicine has recorded its use against insomnia, neuralgia, migraine pain, rheumatism, asthma, bronchitis and loss of appetite.



$R = C_5H_{11}$

Δ^1 - THC

Recently some cancer patients undergoing chemotherapy and using marijuana type drugs as analgesics noticed relief from the nausea that often accompanies this treatment. This observation was clinically confirmed by Sallan and co-workers[2] in 1975 and is very important since many patients die of malnutrition while being treated with anticancer drugs.

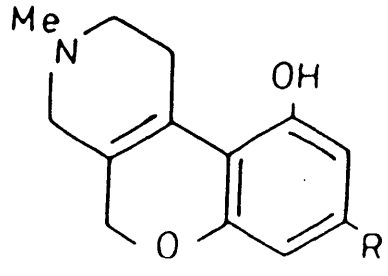
It is unlikely that natural marijuana will become a marketable product because it is a complex mixture of over thirty five known cannabinoids, various terpenes,nitrogen bases, phenolic compounds, sugars etc. It is possible that its main active component Δ^1-THC could become a viable drug, but it is most probable that useful products will come from synthetic analogues in which the undesirable side effects and physical characteristics of Δ^1-THC are modified or eliminated.

The term cannabinoid is used for a group of compounds present in Cannabis sativa L. (family Moraceae), their analogues and transformation products.

1.1.2 Heterocyclic analogues

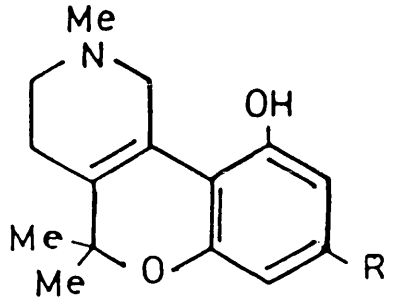
The observations that Δ^1-THC is one of the very few potent drugs that act on the central nervous system (CNS) yet has no nitrogen in its structure resulted in great interest of many chemists to prepare nitrogen analogues.

For example, Anker and Cook[3] have synthesised the analogue (1) and its dihydro derivative only to find that these structures do not possess any analgesic activity.



(1)

However Pars et al[4] reported the synthesis of the analogue (2) and discovered it had a marijuana-like pharmacological profile. Then, since 1966 various nitrogen analogues and sulphur analogues (3) have been made which show various grades of CNS activity in laboratory animals.



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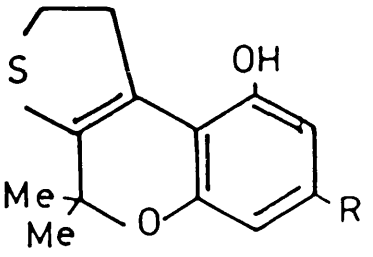
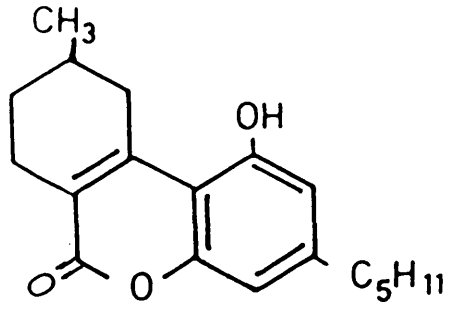
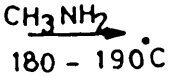
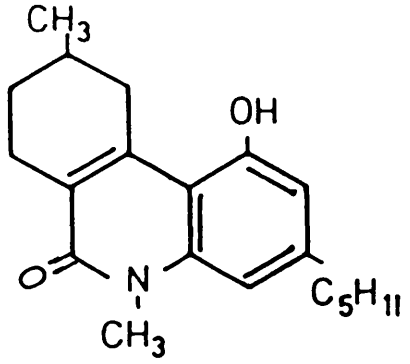


(3)

Another biologically inactive compound is the amide (5), synthesized[5] by replacing the pyran oxygen of (4) with a methylamino group.



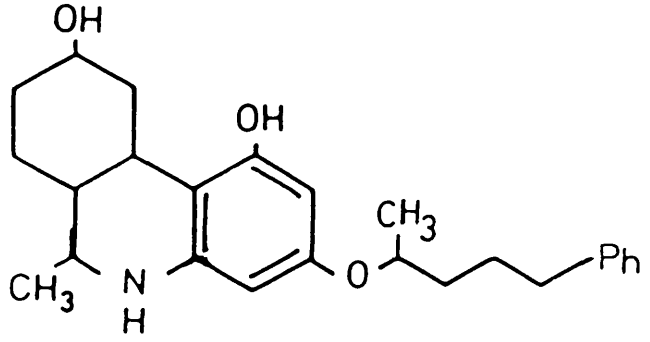




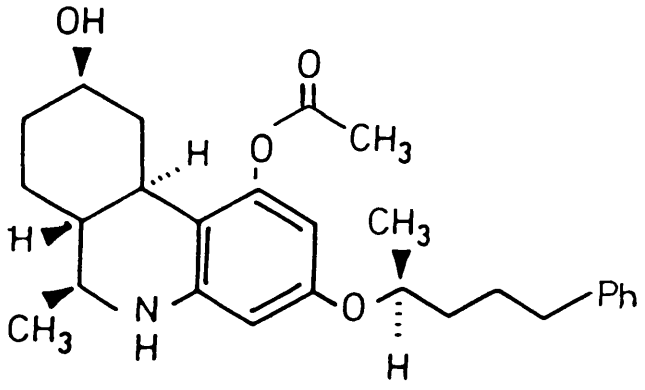
(4)

(5)

However the closely related amines (6) and (7) have been reported to be very active biologically and they have become compounds of considerble interest as potential drugs.

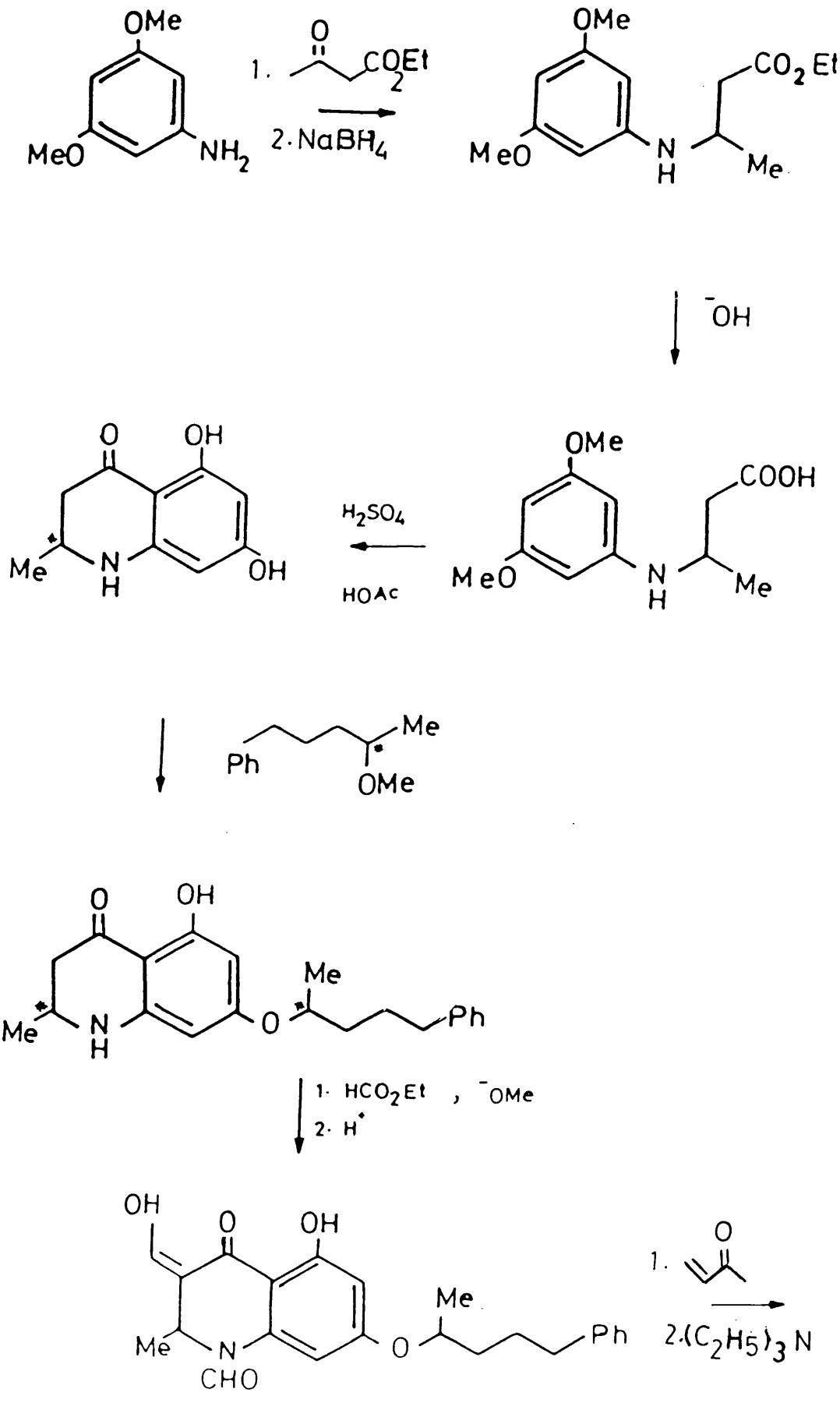


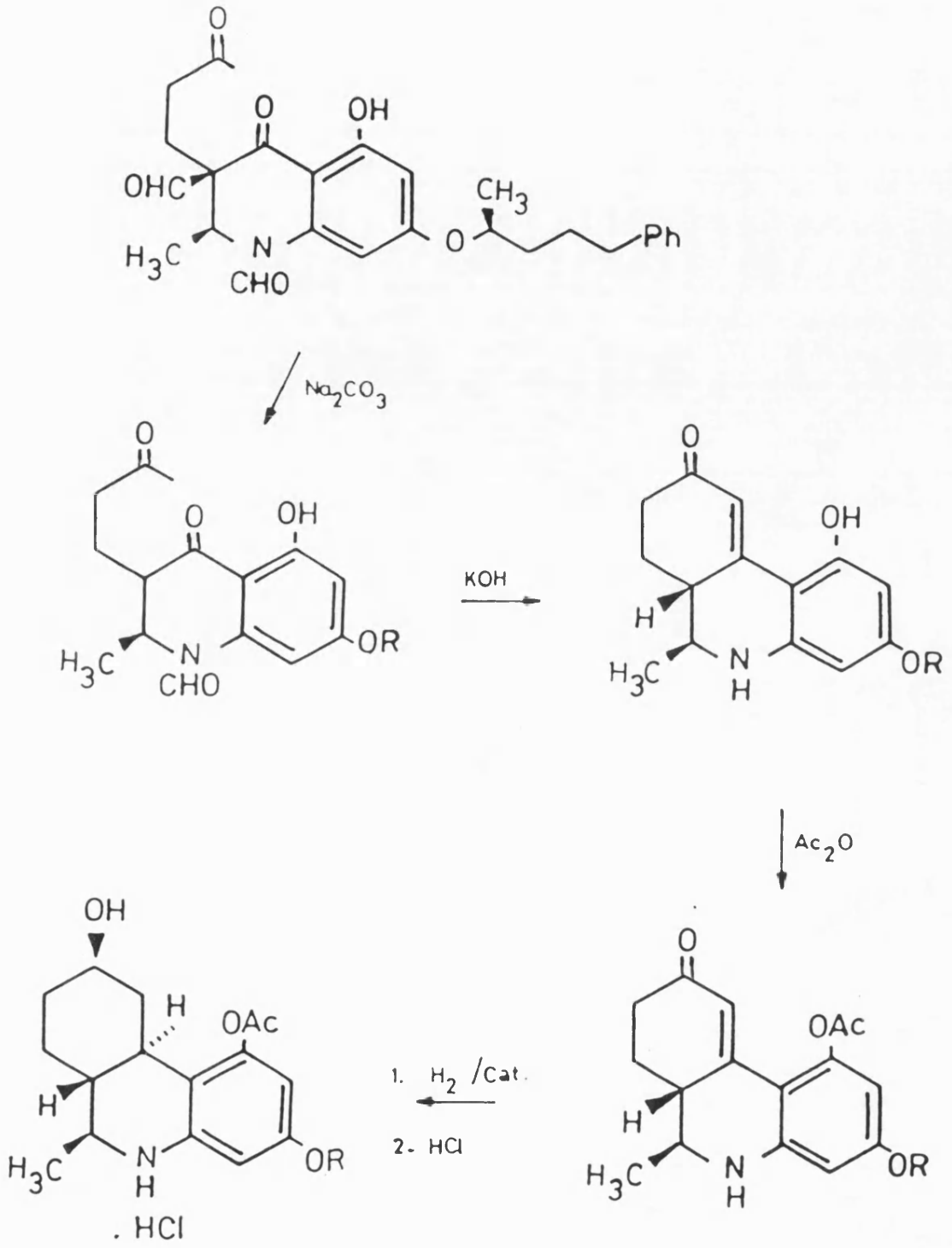
(6)



(7)

Indeed compound (7) is now known as levonantradol and a synthetic route to its hydrochloride salt was reported by Pfizer[6]. This synthesis is illustrated in Scheme 1.


OMe
MeO
NH2
1.
O
COEt
2
2·NaBH4
OMe
MeO
N
H
CO2 Et
Me
OH
O
OH
Me
N
H
OH
H2SO4
HOAc
OMe
MeO
N
H
COOH
Me
Ph
Me
OMe
O
OH
Me
N
H
O
Me
Ph
1· HCO2Et , OMe
2· H+
OH
O
OH
Me
N
CHO
O
Me
Ph
1.
O
2·(C2H5)3 N


O
O
OH
OHC
CH3
H3C
N
O
Ph
CHO
Na2CO3
O
O
OH
KOH
H3C
N
OR
CHO
O
OH
H
H3C
N
H
OR
Ac2O
OH
H
OAc
1. H2 /Cat.
2- HCl
H
H3C
N
H
OR
. HCl
O
OAc
H
H3C
N
H
OR

Scheme (I)

1.1.3 Clinical importance of levonantradol

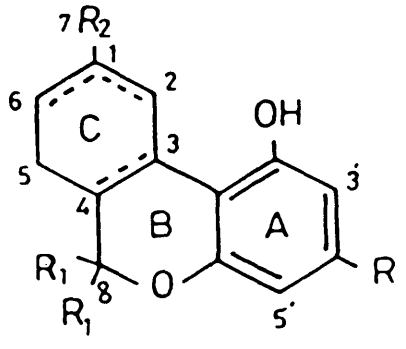
Levonantradol[7] is currently being evaluated clinically for both antiemetic and analgesic effects. In animals levonantradol acts to produce analgetic activity 12 to 30 times greater than morphine. Perhaps the more important use is in controlling nausea, however, and the drug may be given to patients receiving cancer chemotherapy at doses as low as 0.5mg/kg to relieve drug induced sickness.

Complete elimination of nausea and vomiting was attained in some patients, but the majority had only partial control. The overall response rate to levonantradol was 80% compared with 50% Δ^1-THC-treated patients. There are two possible explanations for this:

1. Levonantradol is a more effective antiemetic, or
2. The intramuscular route of administration gives rise to a more uniform absorption of the drug than previous studies using orally administered Δ^1-THC. Dose limiting toxicity include dysphoria and dizziness. Approximately, 15% of patients experienced these latter problems. The dysphoria was characterised by unpleasant feelings of loss of control, anxiety and panic. These symptoms lasted 1 to 4 hours in all patients hence neither sedation nor antipsychotic medication[8] were required by any patients.

1.1.4 Overall structure-activity relationship

The synthesis and demonstration of CNS activity for a wide variety of cannabinoids has resulted in an expansion of the structure-activity hypothesis originally put forward by Adams and co-workers.[9] Referring to the general structure (8) Adams found that the potency was increased when R was a highly branched alkyl group with the 1,2-dimethylheptyl unit showing optimum activity. This author also showed that when R_1 and R_2 were methyl groups the activity of the drug was greater than when they were higher alkyls. Reduction of the double bond in the C-ring retained activity and the C-ring could be contracted, expanded or even opened without losing activity entirely.

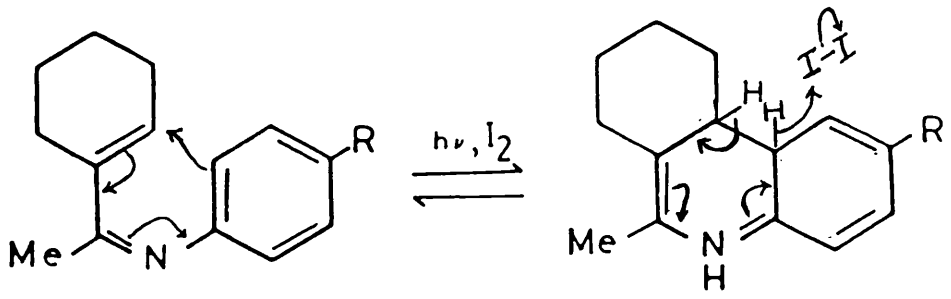


(8)

1.2 Discussion

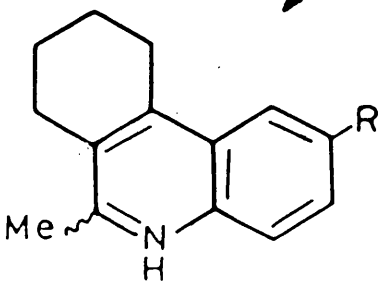
The aim of this research programme was to devise a more efficient synthesis of levonantradol (7) than that shown in scheme 1 (page 5). This route involves ten steps in the synthesis of the octahydrophenanthridine component. In addition, there is a resolution step and four more steps for the construction of the phenyl pent-2-yl side chain. In view of this lengthy approach it was

considered that more successful preparation might involve a key ring-forming proceeding via the photochemical electrocyclisation of imines to give hexahydrophenanthridines. Should this succeed starting materials bearing the appropriate functionalities for conversion into the drug itself could be used, and in order to investigate the viability of such an approach it was decided to examine the cyclisation of the model imines (9) and (10).



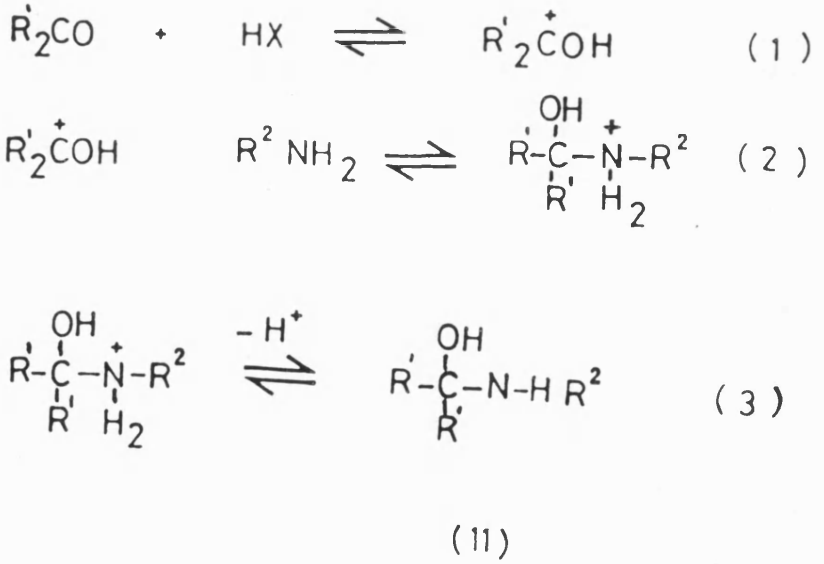
(9) R = H

(10) R = OMe

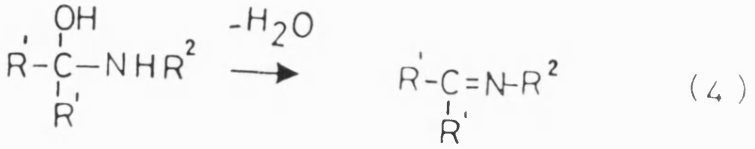


An obvious synthesis of such imines was simply to heat acetylcyclohexene with either aniline or P-methoxyaniline in a Dean and Stark apparatus in a solvent such as benzene containing a catalytic amount of P-toluene sulphonic acid. Surprisingly enough the yields of anils formed were very low 5%, but if the acid catalyst was replaced by a strongly acidic resin amberlyst-15, this yield rose to 25%.

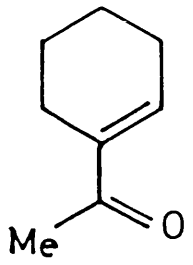
In general imine formation proceeds through the unstable intermediate (11) with the loss of water, and Hammett[10] has proposed that acids protonate the oxygen atom of the carbonyl component to give a carbonium ion which reacts with the amine in a very fast reaction. The rate determining step in the total reaction is the deprotonation of this intermediate to give a carbinolamine (11) which rapidly eliminates water to give the corresponding imine.



(11)

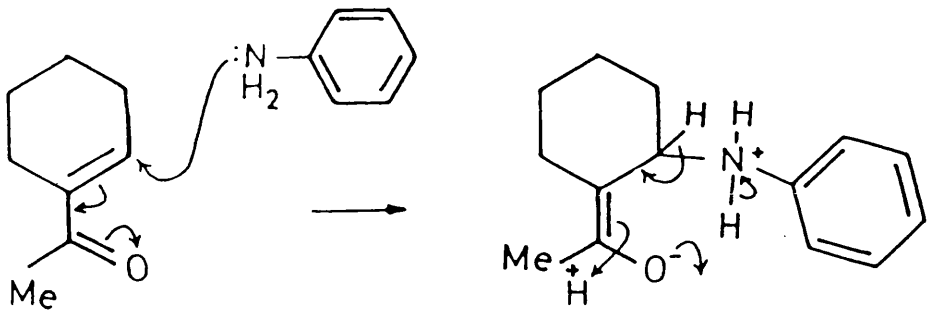


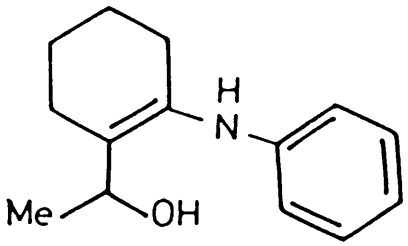
It seems probable that in the final elimination step (4) loss of water is promoted by protonation of the hydroxyl group of the carbinolamine, and since this then leads to the only irreversible step in the sequence the increase in the yield when a stronger acid catalyst is used in our reaction may indicate that the corresponding carbinolaimine is less basic than usual. The enone (12) is a rather weak base relative to many simple aldehydes and ketones.



(12)

A minor component in the reaction between aniline and the enone (12) is the Michael product (13). It proved to be breaking down to the starting components, thus it is possible that it is a major product within the reaction vessel accounting for the low yield of the imine. Certainly tlc analyses indicate all the starting materials to be used up at the end of the reaction time but on work-up these self-same compounds "reappear". In addition we soon discovered that the imine itself is unstable and in the presence of moisture it also decomposed to aniline and the enone.





(13)

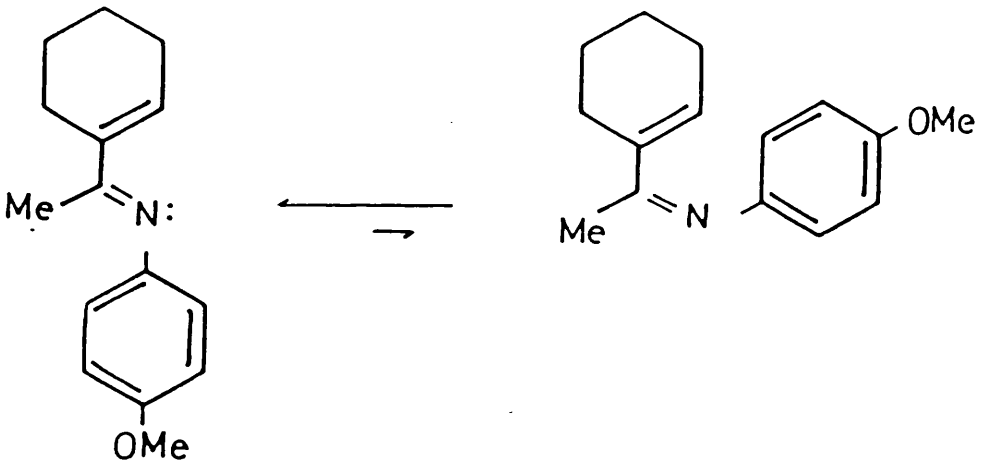
Scheme (2)

The infra-red spectrum of this imine showed a characteristic carbon-nitrogen double bond absorption at ν_{max}=1620cm^{-1}. The mass spectrum indicates a molecular ion peak at m/z 199 which corresponds to the molecular formula $C_{14}H_{17}N$. The ^{1}H n.m.r. spectrum of this anil was recorded at 100 MHz showes a signal due to five aromatic protons as a multiplet at δ6.6-7.3ppm, one vinylic proton resonance as a weak triplet at δ6.5ppm, four aliphatic protons giving rise to a signal at δ2.2-2.46ppm, a sharp singlet arising from the resonance of the methyl group at δ1.89ppm, and another aliphatic multiplet at δ1.35ppm corresponding to the signals of four protons. No assignment of the actual geometry of the imine has been made.

Through a similar reaction the P-methoxylated analogue (10,R=OMe) was prepared. Once again it was purified by column chromatography, and was found to be unstable. The infra-red spectrum of this compound indicates an absorption band at ν_{max}= 1640cm^{-1} which contrasts with that of frequency of its lower homologue and reflects the electronic influence of the P-substituent, its mass spectrum shows a molecular ion at m/z 229 corresponding to the molecular formula $C_{14}H_{19}NO$ and in the H^{1} n.m.r. spectrum (100MHz) shows four aromatic proton signals occur as a multiplet at δ6.4-6.92ppm, sharp singlet δ3.79ppm integrating to three proton signals corresponds to the methoxy group,

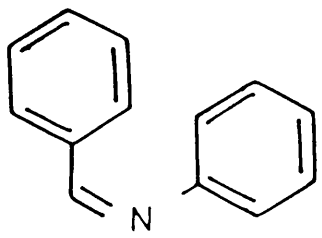
and four aliphatic protons resonate in the region δ2.24–2.42ppm, in addition there is another sharp singlet at δ1.93ppm due to the resonance of the methyl group and four aliphatic proton signals at δ1.75ppm.

Although the results of Nuclear Overhauser effect enhancements were unconvincing it can be inferred that the type of geometry most likely assumed by this compound, is trans simply on thermodynamic basis.



trans cis

The known compound benzylidienaniline (14) was also synthesised for use in some model cyclisation reactions to be discussed later. Unlike the other two imines, already mentioned, benzylideneaniline was very easily prepared, and was much more stable than either of the other imines because of the presence of a highly conjugated system.



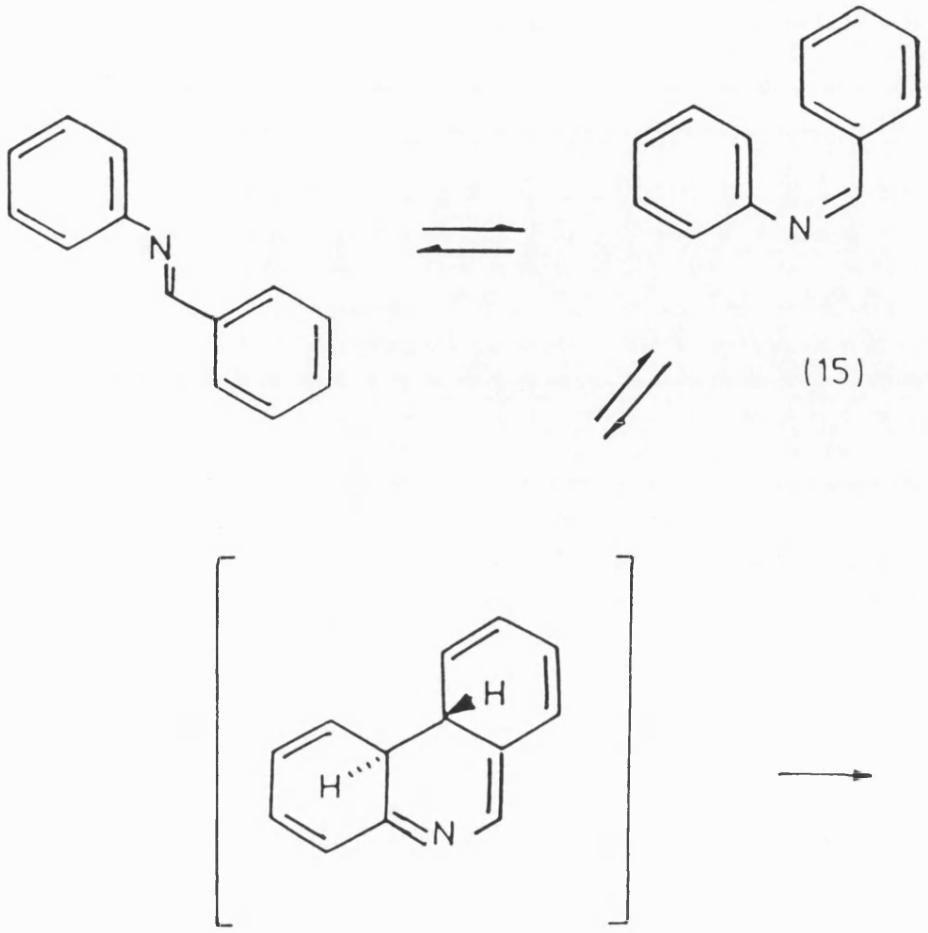
(14)

1.2.1 Reactions of imines

1.2.1.1 Photochemical reaction

In a review by Pratt[12] on the photochemistry of imines, he reported that alkyl imines exhibited two major absorption bands in the ultra-violet absorption spectrum. A short wavelength absorption at λ 170–180nm of high intensity is believed to involve a $\pi \rightarrow \pi^*$ transition, whereas the second less intense band, at λ 230–260nm is considered to result from an $n \rightarrow \pi^*$ transition. Excitation of the latter wavelength region is much more commonly used in preparative work as it is most readily accessible. Aryl substituted imines absorb at longer wavelengths, because of conjugation and their spectra are complex. In such cases the number of bands observed and their positions depend on the nature of the aromatic substituents present, and the bands are assumed to be of both localised $\pi \rightarrow \pi^*$ and charge transfer types. It is known that the ultraviolet spectrum of benzylideneaniline exhibits an intense maximum at λ_{max} 252nm and a shoulder at λ_{max} 315nm. The expected $n \rightarrow \pi^*$ bands are, in fact, symmetry forbidden and their extinction coefficients are low .

As mentioned before we assumed that, regardless of the stereochemistry of the parent imine, enough of the cisoid form would be generated on irradiation with ultraviolet light to allow the development of a transition state leading to a typically allowed conrotatory cyclisation to a dihydrophenanthridine (16). If

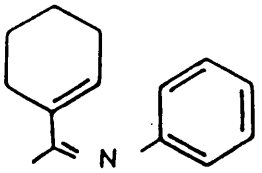


(15)

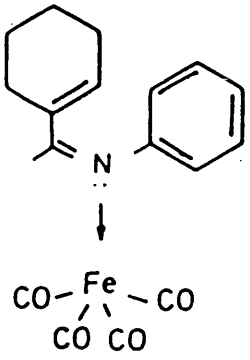
(16)

(17)

Scheme (3)

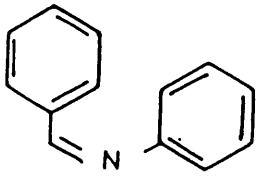


$Fe_2(CO)_9$ $\xrightarrow[\sim 40^\circ C]{C_6H_6}$ N_2

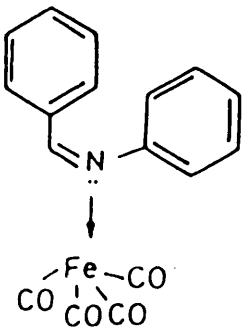


(18)

Scheme (4)



$Fe_2(CO)_9$ $\xrightarrow[RT]{C_6H_6}$ N_2



(19)

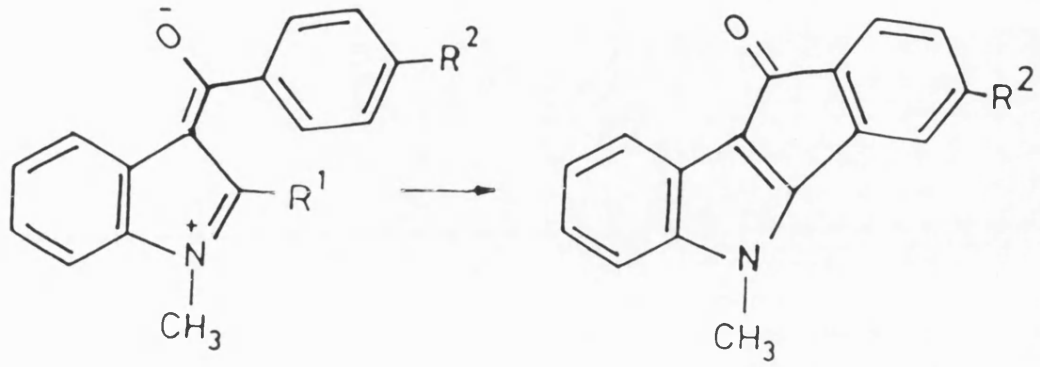
Scheme (5)

oxygen, or an oxidant, were present then the product would be irreversibly oxidised to the phenanthridine (17), see scheme 3, and the whole reaction sequence would be polarised towards this end result.[13]

Unfortunately we discovered that irradiation of the imine in organic solvents did not lead to such a phenanthridine. In fact others too have reported such a failure[14]. Only if the reaction medium is very strongly acidic does the reaction succeed and it may be that protonation of the nitrogen atom is an important prerequisite. The use of concentrated sulphuric acid as a solvent was not viewed as a practical way out of this problem, but rather it was speculated that if suitable N-metal complexes could be made, the same effect might result. In fact N-tetracarbonyliron complexes of both of the imines (9) and (14) were prepared (see schemes 4 and 5).

Iron-complexes of the imines (9) and (14) were prepared but, unfortunately, both these complexes were highly unstable and were rapidly decomposed back to the starting imines when left exposed to light. Hence, in the course of their identification the only available data was their infra-red spectra and for both imines vibration frequencies of the four iron-carbonyl bands were

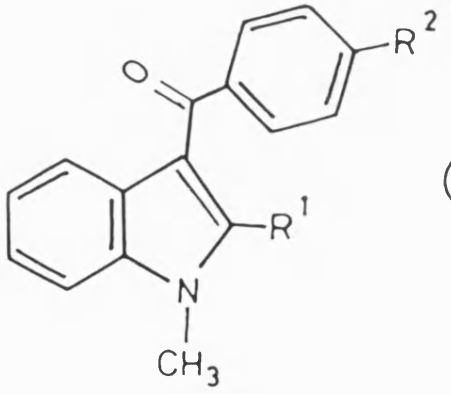
Scheme (6)



$Pd(OAc)_2$
AcOH
Δ 110°
N_2

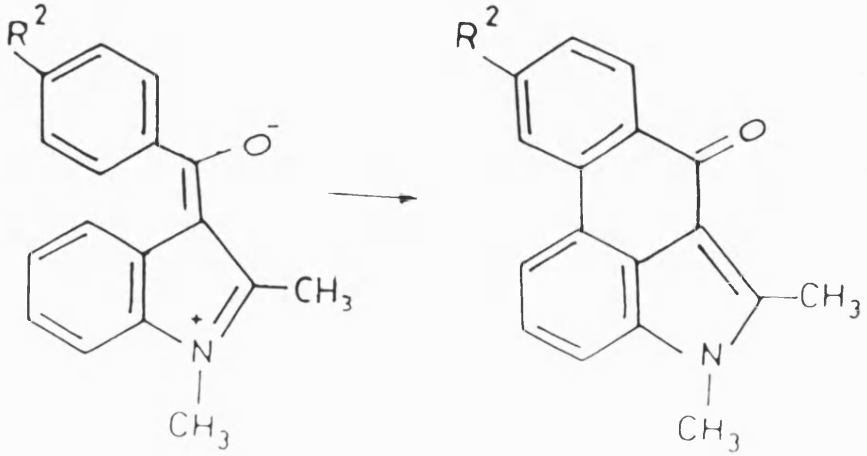
$R^1 = H$

(21)



(20) a R^1 $R^2 = H$
b $R^1 = CH_3$ $R^2 = H$
c $R^1 = R^2 = CH_3$

$R^1 = CH_3$



(22) a $R^2 = H$
b $R^2 = CH_3$

observed. The carbonyl stretching band of the complex (18) occurred at ν_{max} 2050, 2025, 1983 and 1962cm^{-1} and for the complex (19) similar absorptions were exhibited at ν_{max} 2075, 2040, 1995 and 1945cm^{-1}.

These results wre not unexpected for Cardaci[15] as previously shown that nitrogen of the complexes of tetracarbonyliron with imines are not stable.

Itahara[16] and Sakakibara have reported the use of palladium(II)acetate in intramolecular ring closure of 3-benzoylindoles (20a-c). This work followed their unsuccessful photochemical attempt to cyclise (20a-c). Treatment of (20a) in acetic acid with 0.5 equivalent of palladium acetate under nitrogen gave 5-methyl-5,10-dihydroindeno[1,2-b]indol-10-one (21) in 60% yield. Under similar conditions 3-benzoyl-1,2-dimethylindole (20b) reacted to give a polycyclic indole, 4,5-dimethyl-4,6-dihydronaphth[3,2,1-c,d]indol-6-one (22a) in 31% yield. Furthermore, the oxidation of 1,2-dimethyl-3-p-methylbenzoylindole (20c) by palladium acetate yielded (22b) in 23% yield, see Scheme 6.

Attempted intramolecular coupling reactions of benzophenone and benzil, however, failed under similar conditions. Hence, these authors concluded that the rigid β-amino-α,β-unsaturated ketone structure of (20) might facilitate the intramolecular coupling.

We carried out this type of reaction using N-benzylideneaniline which gave a 20% yield of the phenanthridine. However, no cyclised products were obtained in the case of the imines (9) and (10).

The low yield of the phenanthridine did not allow full analysis of the structural data. However, the melting point of this compound and mixed melting point of 104°C was close to the literature value[27] of 104°C.

At this point we concluded that this approach to the required octahydrophenanthridines was unlikely to be successful and abandoned the project in favour of some different but related work.

A NEW APPROACH TO THE SYNTHESIS OF ERGOT ALKALOIDS

2.0.1 INTRODUCTION

2.0.1.1 A general background on ergot alkaloids

Ergot (Secale cornutum) is the product of a filamentous fungus Claviceps purpurea[17,18] that grows parasitically on rye and other plants of the Gramineae family. The rye grains attacked by the fungus develop into dark brown, horn-shaped pegs projecting from the ripening ears. Under the microscope this is seen to consist of interwoven hyphae forming compact grains known as sclerotia, in which form the fungus passes the winter.

The fungus Claviceps purpurea and related species also attack other genera of the Gramineae giving rise to sclerotia, the shape and size of which vary with the species of the host plant. The best known form of ergot, however, is the product that forms on the ears of rye.

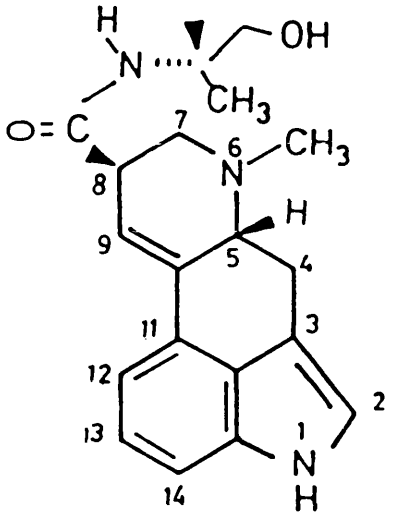
Long before ergot was discovered to be a rich source of therapeutically useful alkaloids it often played a tragic role in being the cause of devastating poisoning epidemics called in the middle ages "St Antony's Fire". The history of ergot and ergot poisoning has been described by Barger.[26]

The extensive use of ergot alkaloids as medicaments has resulted in a substantial increase in the demand for ergot, a demand that has for many years exceeded the naturally available supply. The major portion of the

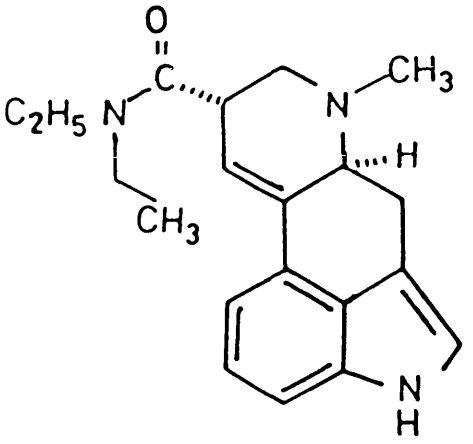
naturally grown ergot originally came from Spain and Portugal where, in good summers, crops of over one hundred tons were obtained. Of late, the ergot fungus required for the industrial production of ergot alkaloids is to a large extent cultivated artificially on rye and also *in vitro* on saprophytic cultures.

In the case of the parasitic cultivation of ergot on rye, the rye ears, when in bloom are infected with a suspension of the fungus obtained by culture either by spraying or, more effectively, by injection. For the purpose of industrial scale production, innoculation machines which permit large fields to be infected by the injection method are currently being used.

The cultivation of the ergot fungus on artificial nutrient media has also been developed. Originally, it was only possible to produce alkaloids *in vitro* with fungi of the *Claviceps* type that grew on wild grass. Most of these alkaloids are of the clavine type which have found no therapeutic application. The first step of commercial significance in this area was the discovery of the fungus strain *Claviceps paspali* (Stevens and Hall) which in culture is capable of producing considerable amounts of lysergic acid derivatives especially lysergic acid amide and isolysergic acid amide[19]. These natural products and drugs made from them are known collectively as the ergot alkaloids, and have found use in medicine. Ergonovine[20] for example, is a selective stimulant for contraction of uterine muscle and is used to assist with labour and subsequent infant delivery.



Ergonovine



d-LSD - 25

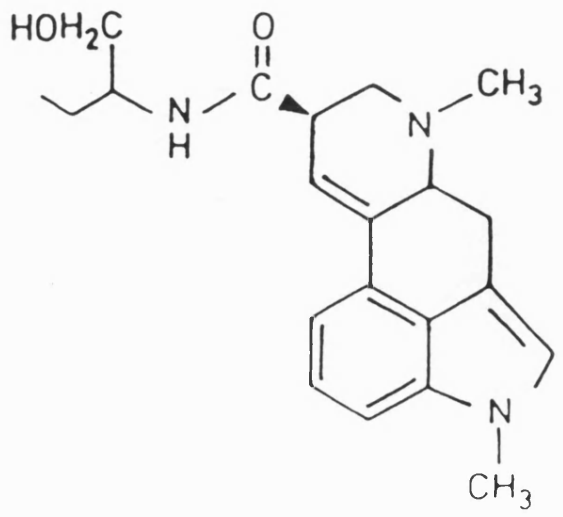
A mixture of hydrogenated ergot alkaloids reduced at the 9,10-positions has found use as a cerebral vasodilator by reason of its α-adrenergic blocking activity.

The discovery of the potent hallucinogen LSD-25[21], represents one of the classic cases of serendipity. In the course of an analogue programme on lysergic acid derivatives in the Sandoz laboratories in Switzerland, Hofmann had occasion to prepare the simple diethylamide derivative. On his way home from work that day, he saw the city of Basle in an entirely new light. The fantastic potency of the compound had led him to ingest sufficient drug as dust to experience the hallucinogenic effect.

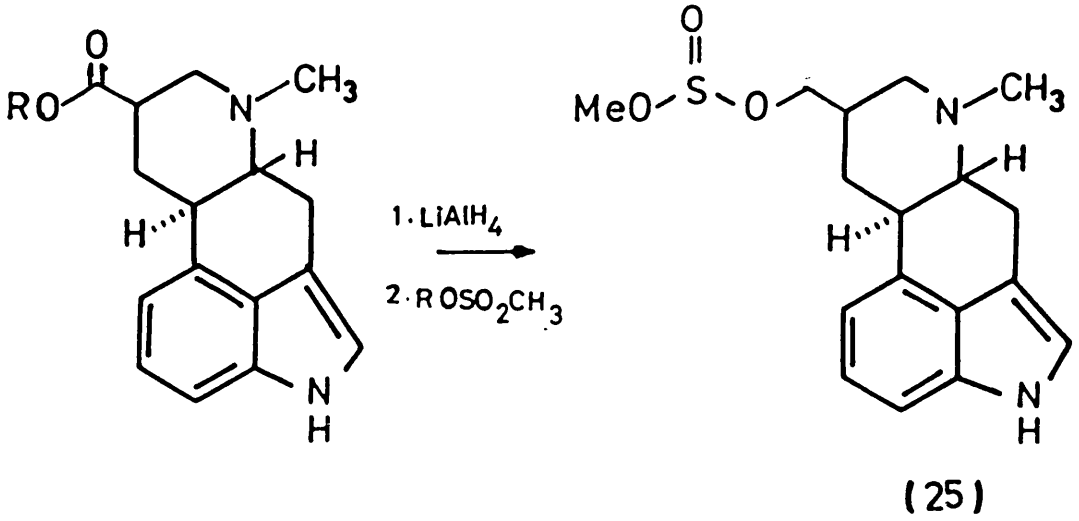
Recognizing the probable cause of his "trip", he verified the effect by deliberately taking a second dose. This is one of those interesting cases where animal pharmacology and toxicology came after the human trial.

A number of hallucinogens, including LSD-25 enjoyed considerable vogue in the counterculture of the late nineteen sixties, but there was no legitimate source for the drug since no recognised clinical use existed then.

Migraine is a particularly virulant form of headache[20] that is suffered by the majority of mankind; the common remedies, such as aspirin, are all but useless against these attacks. Although the exact aetiology of migraine is not known, an attack does involve at one stage dilation of the cerebral vasculature and since the skull is a bony case that cannot accommodate volume expansion of any magnitude, pain ensues. Methysergide, a lysergic acid derivative, which acts as a cerebral vasoconstructor has proven of use in treatment of migraine.

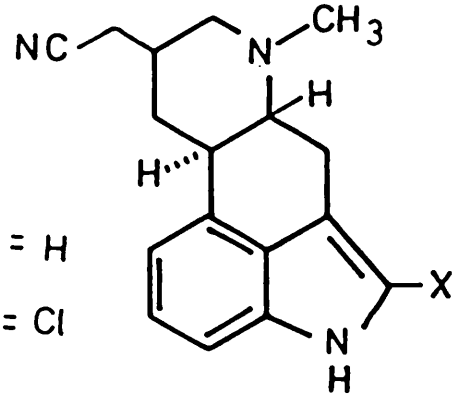


Methysergide



(23) R = H

(24) R = CH_3



(26) X = H

(27) X = Cl

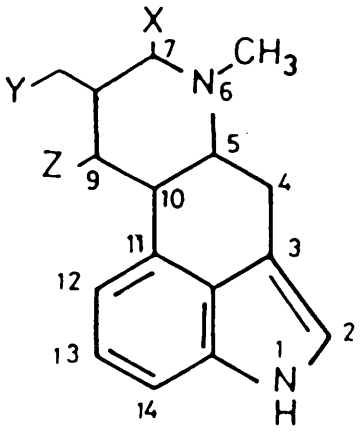
Scheme (7)

Another elaboration of the same molecule affords a compound (27) that acts as an inhibitor of the pituitary peptide hormone prolactin, the factor responsible for supporting lactation. As such the drug has found use in suppressing lactation and in the treatment of prolactin-dependent breast tumors. In the synthesis of the chloro-derivative (27), catalytic hydrogenation of lysergic acid proceeds from the less hindered side of the molecule to give the derivative with the trans-ring junction (23). As above, the reduction of the methyl ester (24) gives the corresponding carbinol. This is then converted to the methane sulfonate (25), and that

function is displaced with cyanide ion to afford the acetonitrile derivative (26). Chlorination with N-chlorosuccinimide at the activated indole 2- position gives the corresponding chloro compound, the prolactin inhibitor, known as lergotrile, see Scheme 7 .

2.0.1.2 Synthetic routes to the ergot alkaloids[28]

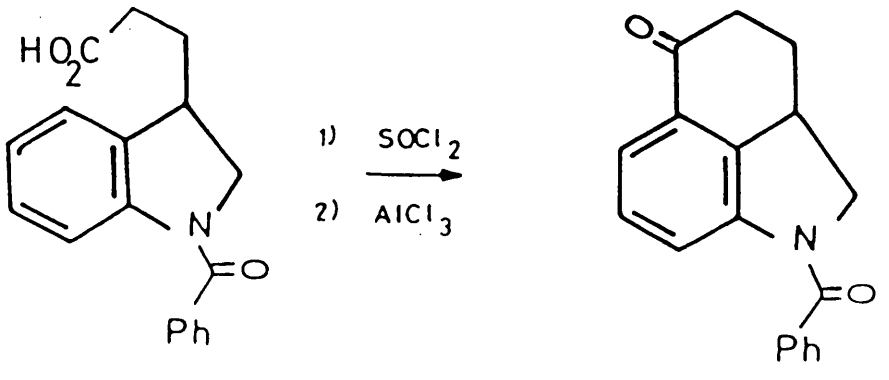
As Kozikowski[22] described in his review, in planning a synthesis of an ergot alkaloid one must eventually decide how the bond linking carbon atoms 10 and 11 will be made.



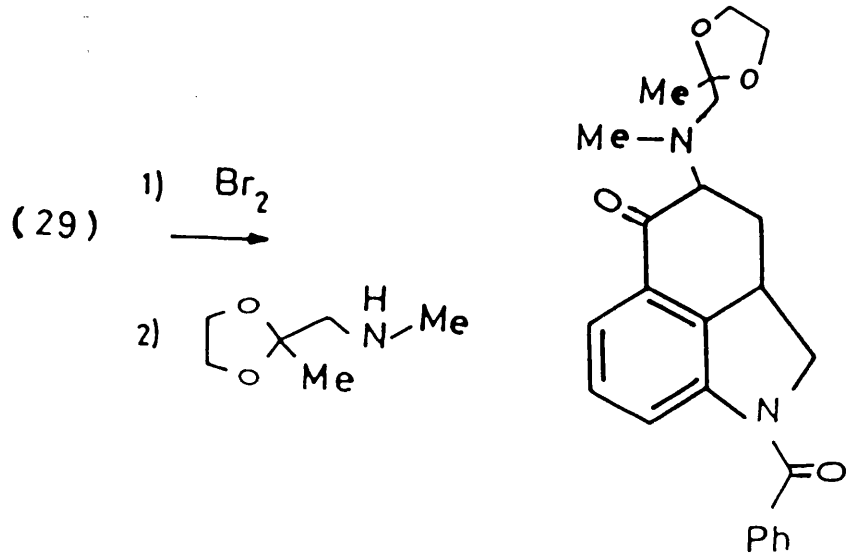
The direct introduction of a carbon unit as an electrophile into the 4-position of indole is difficult to achieve, for this position is more electron deficient than other available sites. Kornfeld and Woodward[23] were able to solve this problem by carrying out an intramolecular Friedel-Crafts acylation reaction on the reduced and N-protected derivative of 3-(indol-3-yl) propionic acid, the N-benzoylindoline (28).

The Kornfeld[23] synthesis of lysergic acid, shown in Scheme 8 , was one of the earliest approaches to an ergot alkaloid. Details of this synthesis are as follows:

N-Benzoylindolinyl-3-propionic acid (28) was converted into the acid chloride and cyclised intramolecularly to give the tricyclic ketone (29). Bromination to yield the α-bromo ketone was followed by reaction with methyl aminoacetone ethylene ketal to form (30). Acid hydrolysis afforded the corresponding methyl ketone (31) and this was cyclised with sodium methoxide to give the tetracyclic, unsaturated ketone (32). The secondary amino group in this structure was protected by acetylation and the ketone reduced with sodium borohydride to give a secondary alcohol (33) which in turn was converted to the corresponding chloride with thionyl chloride in liquid sulphur dioxide. Treatment with sodium cyanide in liquid hydrocyanic acid then yielded the nitrile (34), which was converted by methanolysis to the corresponding ester. This was then subjected to alkaline saponification to form 2,3-dihydrolysergic acid. Dehydrogenation with deactivated Raney nickel in an aqueous solution in the presence of sodium arsenate yielded racemic lysergic acid (35).



(28) (29)



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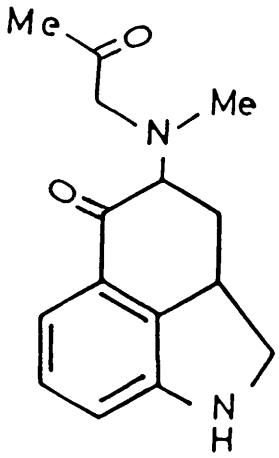
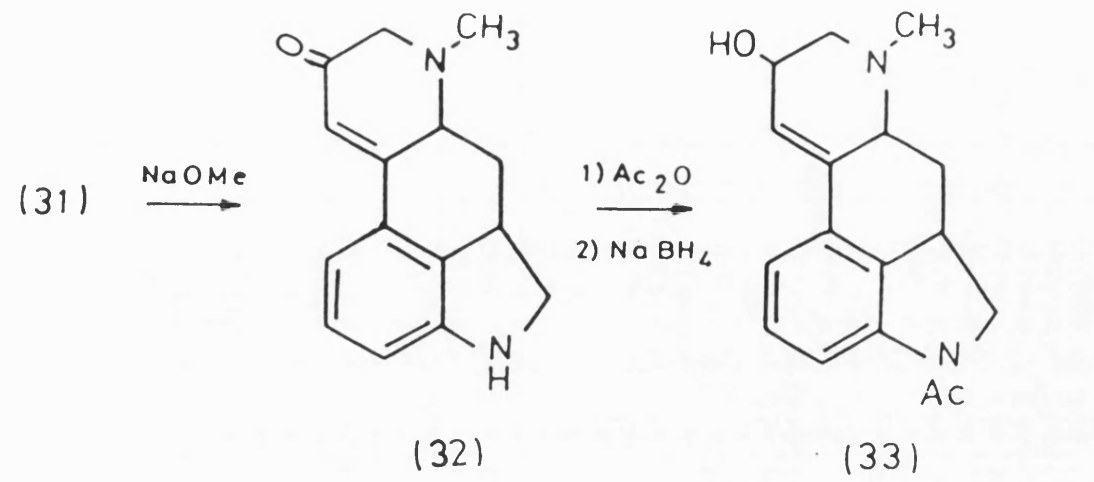
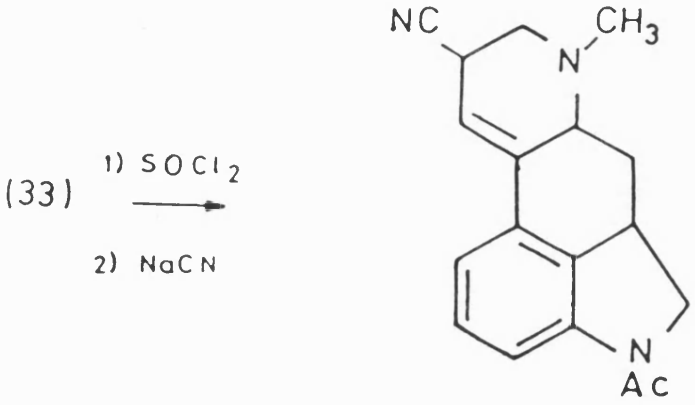


(31)

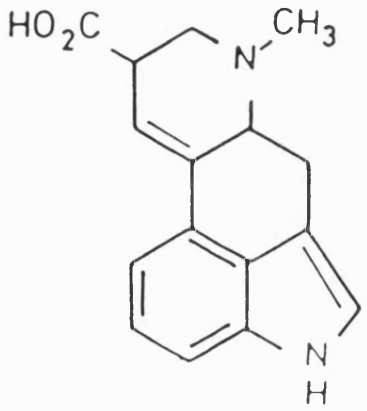


(32) (33)



(34)

1) CH_3OH / H_2SO_4
2) NaOH
3) Raney Ni - H_2O - Na_2AsO_4



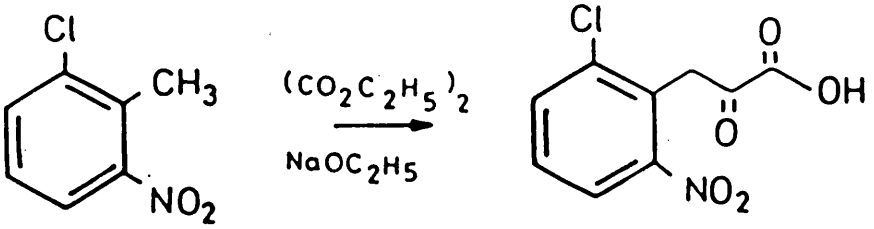
(35)

Scheme (8)

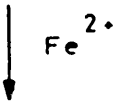
The Kornfeld route therefore accomplished functionalisation at the 4-position of the indole but it had limited use in the sense that many other functionalities could not be introduced easily into C-10 position so as to gain access to a wide range of known ergot structures.

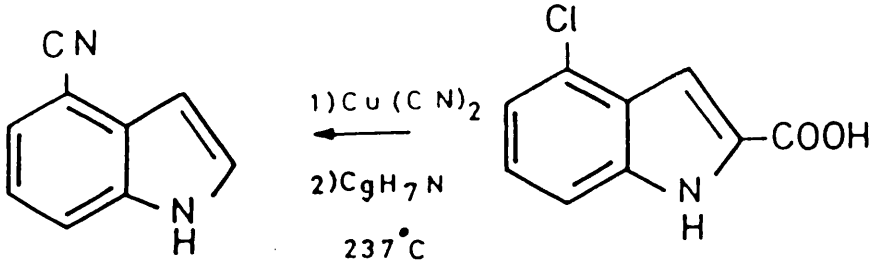
The more popular solution to this problem involved direct synthesis from appropriately substituted arenes. For example, one of the earliest, workable methods to be recorded was designed by Uhle[24] and was based on an extension of the Reissert indole synthesis. This author condensed the readily available dye stuff 2-chloro-6-nitrotoluene with ethyl oxalate to afford a pyruvic acid derivative (36). This derivative was reduced with ferrous hydroxide to give 4-chloro-2-indole carboxylic acid (37). Decarboxylation and replacement of the halogen atom by cyanide occurred on heating this product with cuprous cyanide in quinoline to give (38). This compound was converted through the Mannich base (39) and the malonic ester derivative (40) to β-(4-carboxy-3-indolyl) propionic acid (42). It was eventually found that when a dilute solution of this product in acetic anhydride containing a catalytic quantity of potassium cyanide was maintained at reflux temperature for an extended period and the reaction product hydrolysed with alkali, a good yield (80%) of the ketone (43) was obtained. A modified Wolff-Kishner type reduction with hydrazine and potassium hydroxide in di-ethylene glycol, or a Clemmnsen reduction, led to the formation of the tricyclic structure (44). See Scheme 9 .

Uhle's Synthesis

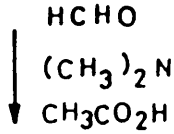


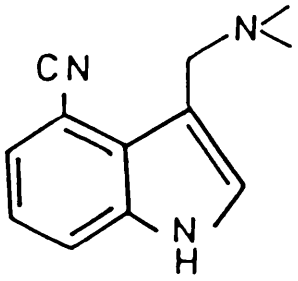
(36)



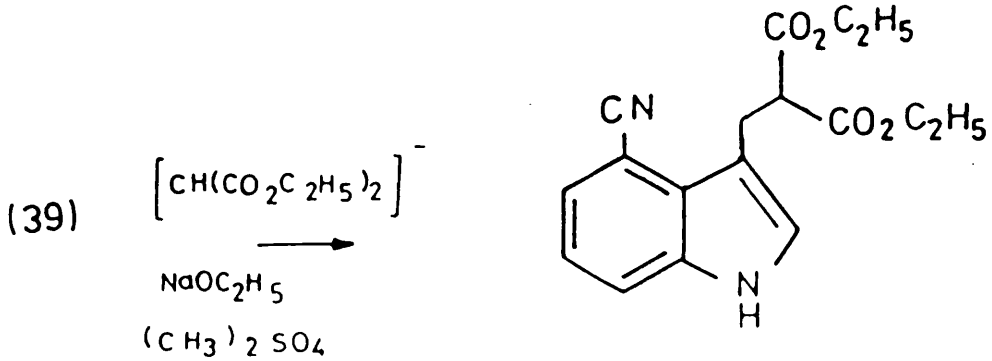


(38) (37)





(39)



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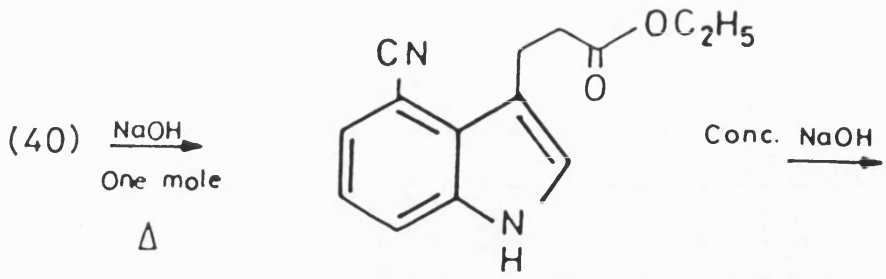

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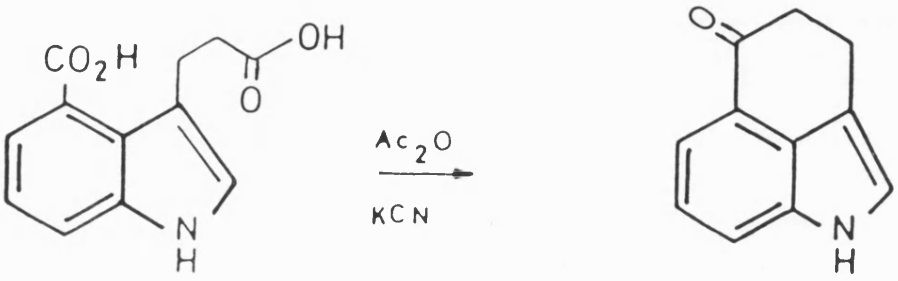
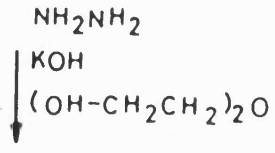
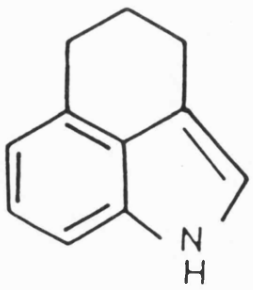


(42) (43)

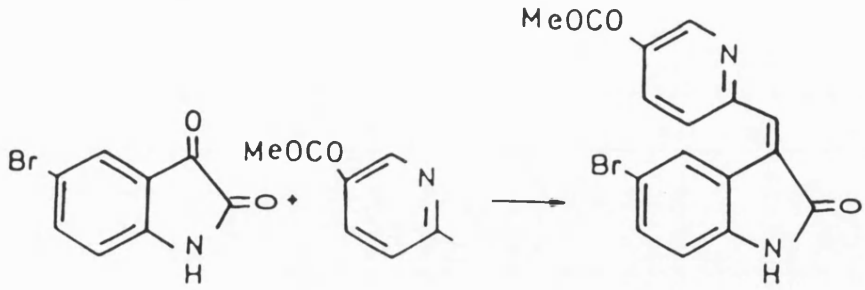




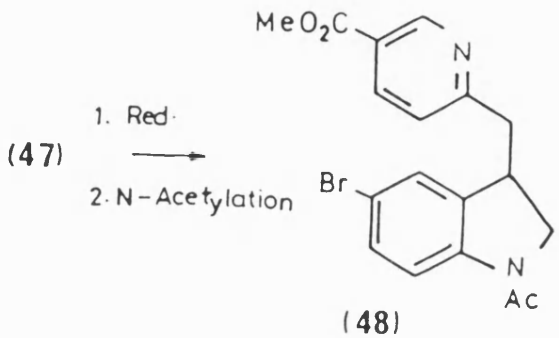
(44)

Scheme (9)

The Julia Synthesis

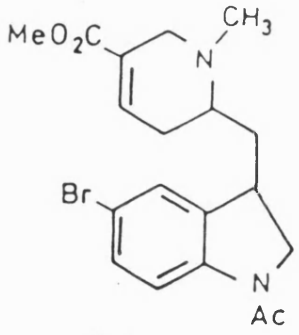


(45) (46) (47)



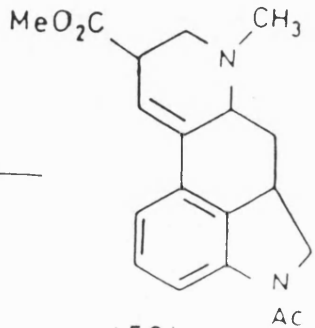
(47) 1. Red. 2. N-Acetylation (48)

N-methylpyridinium salt
KBH_4



(49)

$NaNH_2$
NH_3



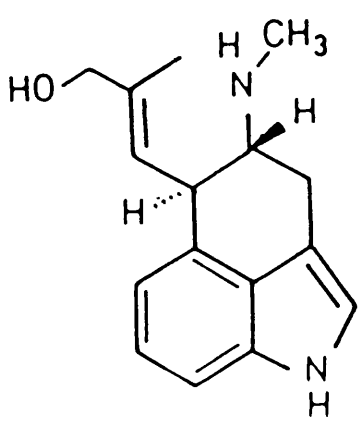
Lysergic acid ← (50)

The Julia[25] synthesis proceeded as follows:

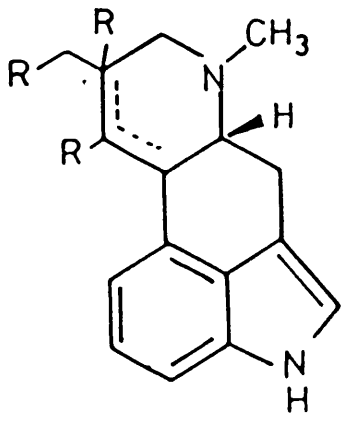
5-Bromoisatin (45) was condensed with the methyl ester of 6-methylnicotinic acid (46). Reduction of the oxindole product (47) to the corresponding indoline (48) and N-acetylation were then carried out. The pyridine ring was reduced by treatment of the N-methylpyridinium salt with potassium borohydride, and the resulting tetrahydropyridine (49) was reacted with sodium amide in ammonia to generate the key tetracyclic system (50) in 15% yield. This synthetic scheme was thus related conceptually to that used by Kornfeld in that the bond between atom C-10 and C-11 was made by an intramolecular mechanism. Here, however, the strategic reaction consisted of the addition of a carbanion to aryne. The synthesis of lysergic acid was completed by an acid promoted ester hydrolysis and N-deacetylation, followed by oxidation of the indoline ring.

The clavines (52) are a class of ergot alkaloids which have slight structural differences to that of lysergic acid. They are substituted 6,8-dimethylergolines and include a few members, named chanoclavines (51). Although, it has been observed that the peptide-type ergot alkaloids generally possess more potent pharmacological activity than those of the clavine type. However, it has been found that the clavine exhibit lower toxicity.

Chanoclavine I

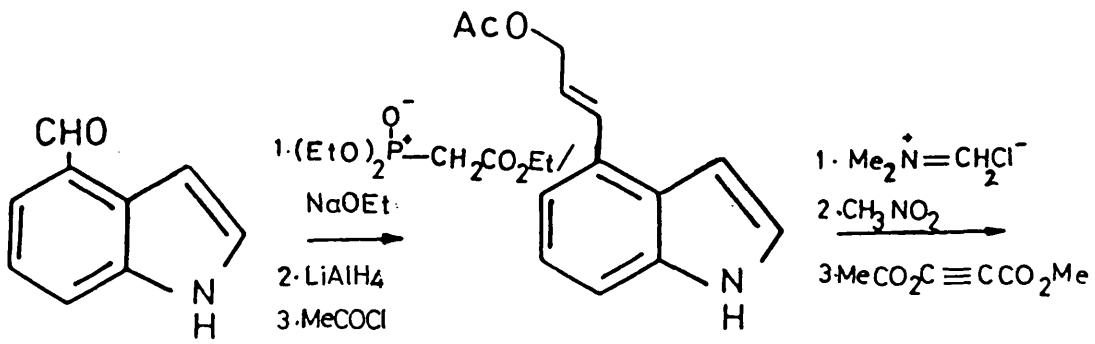


(51)

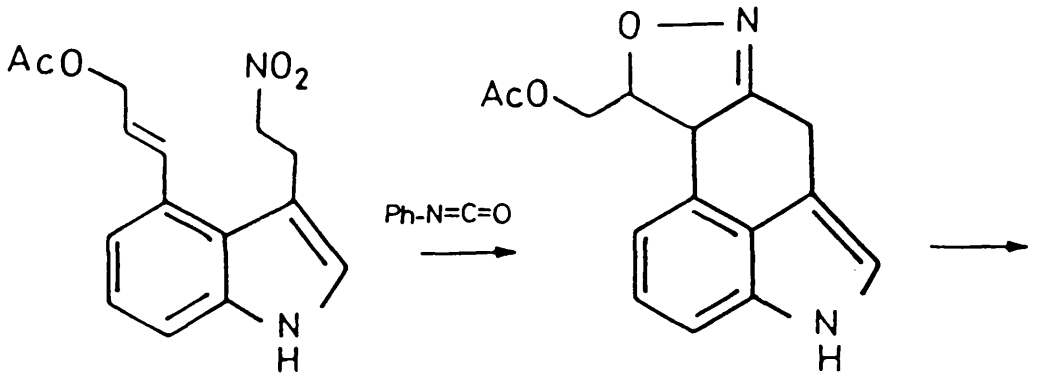


(52)

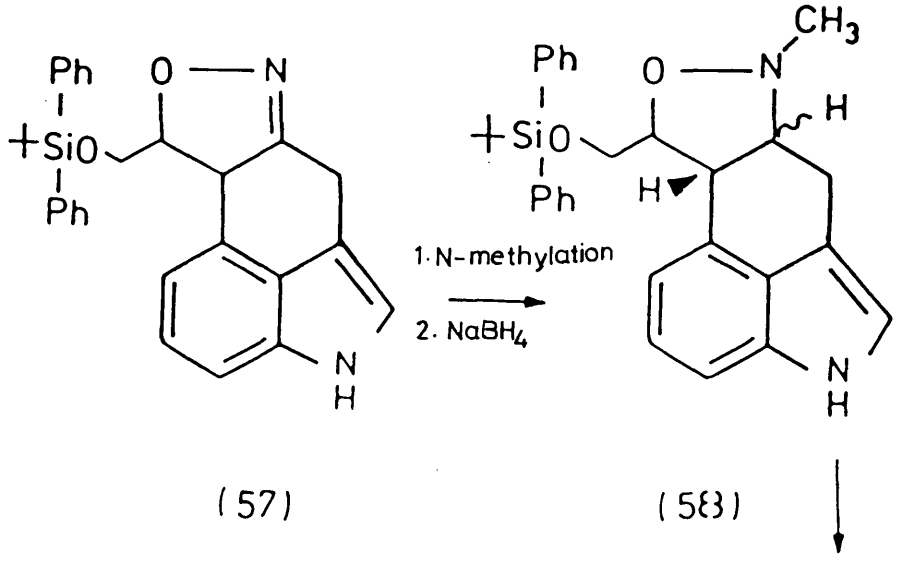
The work of Kozikowski[30] in this area had led to the development of a very general scheme for ergot synthesis. A scheme by which many of the known ergot structures could be introduced. The work had started with the total synthesis of chanoclavine I. This scheme differed from those already discussed in that the strategic step involved bond formation between carbon atoms 5 and 10. Indole-4-carboxyaldehyde, prepared from 2-methyl-3-nitro-benzoic acid, served as the starting agent. This aldehyde was converted into (54) by reaction with the anion of ethyl diethylphosphonoacetate, followed by aluminium hydride reduction and O-acetylation. Reaction of vinylindole (54) sequentially with N,N-dimethyliminium chloride and nitromethane in the presence of excess dimethyl acetylenedicarboxylate gave the 3,4-disubstituted indole (55) in good yield. On stirring with phenyl isocyanate, the nitro group of (55) was converted to a nitrile oxide which was intercepted by the neighbouring unsaturated linkage to afford an isoxazoline. After interchange of the hydroxyl protecting group, the isoxazoline was transformed to isoxazolidine (58) by N-methylation, followed by sodium borohydride reduction. Scission of the N-O bond of (58) by catalytic reduction, acetylation of the amine, and periodate cleavage of the diol unit gave the sensitive key aldehyde (60). Condensation of this aldehyde with ethyl 2-(triphenylphosphoranylidene) propionate, N-deacetylation and aluminium hydride reduction of the ester completed the synthesis. See Scheme 10.



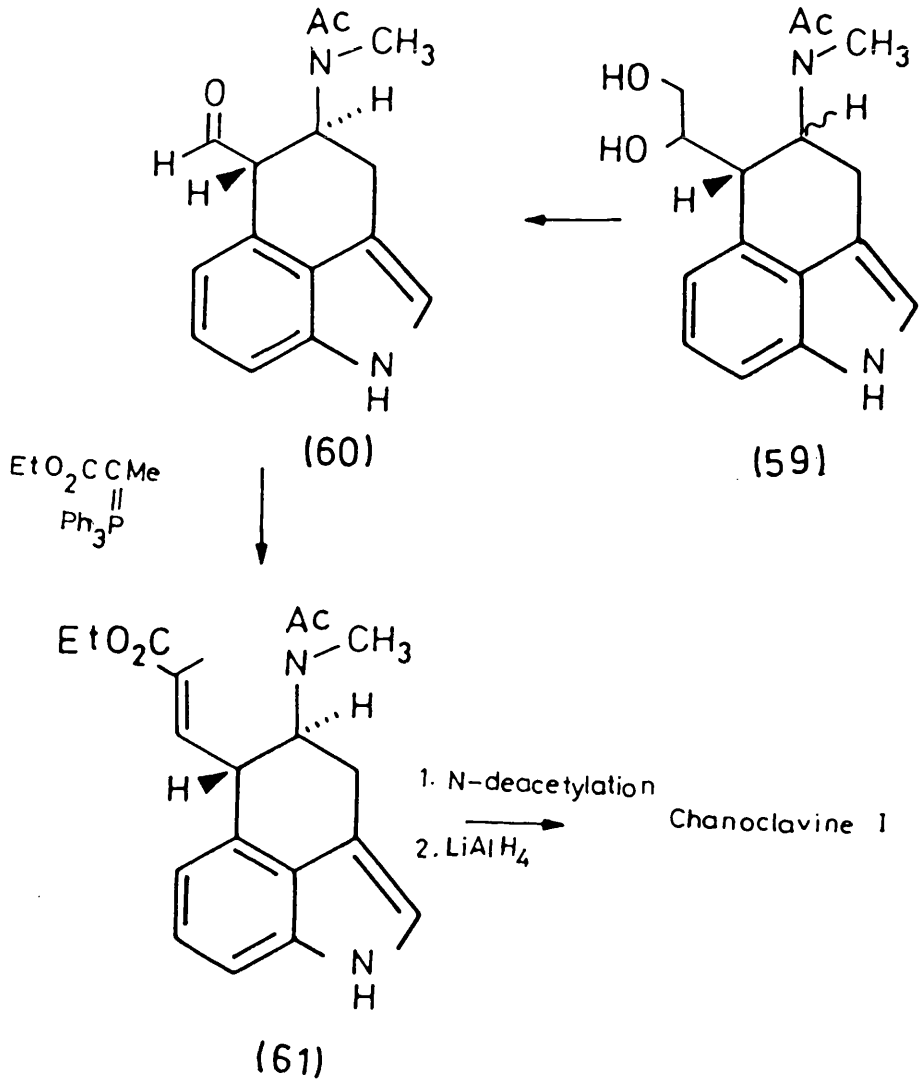
(53) (54)



(55) (56)

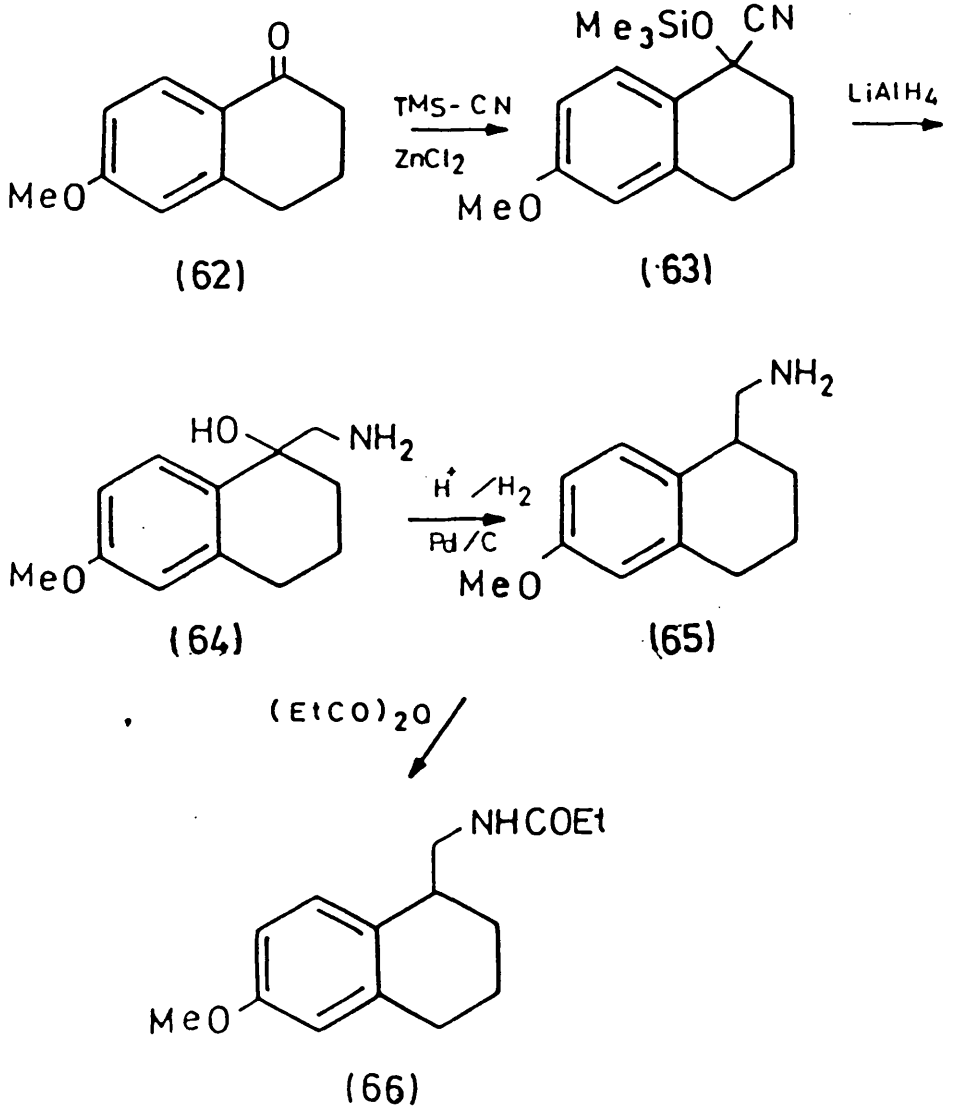


(57) (58)


Ac
N
CH3
H
O
H
H
N
H
(60)
HO
HO
(59)
EtO2CCMe
Ph3P
EtO2C
1. N-deacetylation
2. LiAlH4
Chanoclavine I
(61)

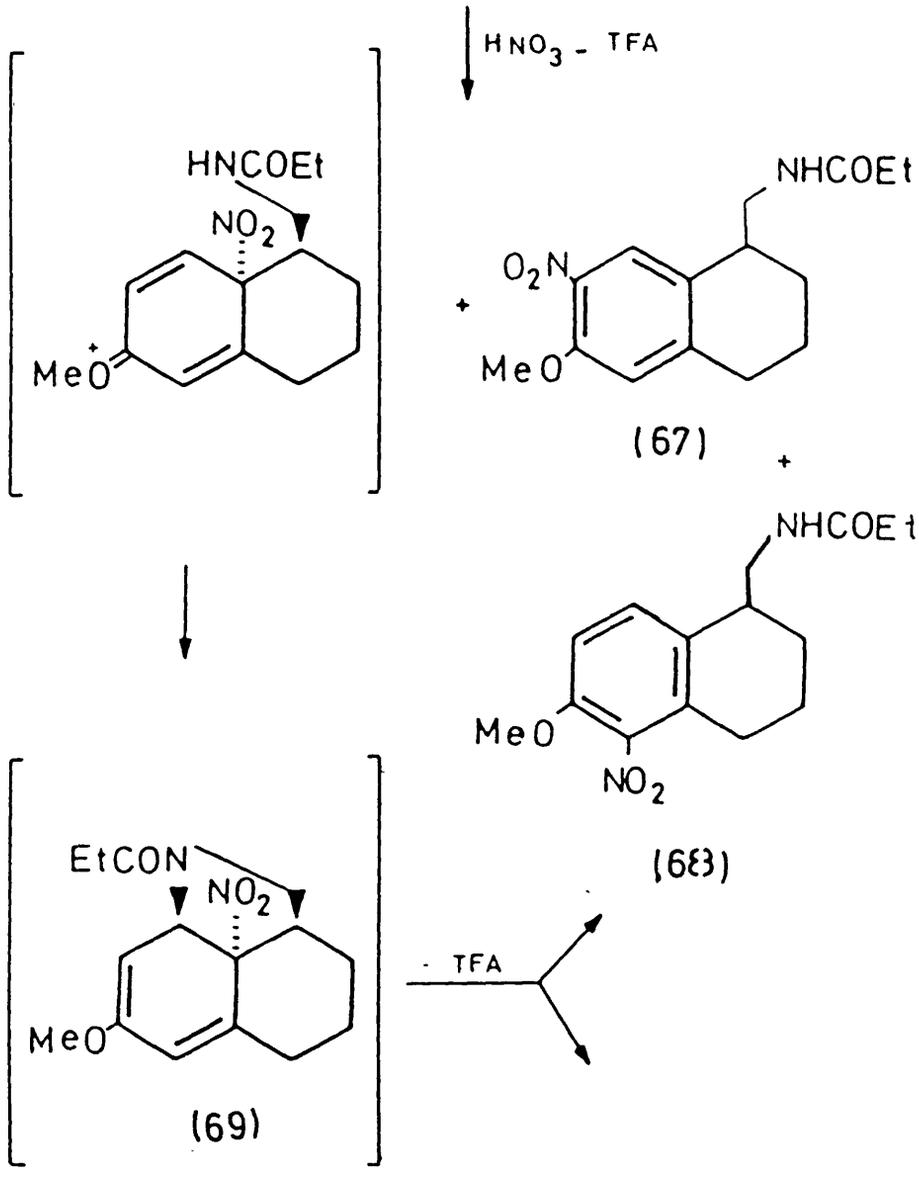
Scheme (10)

Beeley[31] has found recently that his synthesis of novel cardiovascular agents gave not only the expected products (67) and (68) but also the tricyclic adduct (70) which has the ergoline unit structure. This adduct was produced on exposure of N[(6-methoxy-1,2,3,4-tetrahydronaphthalene-1-yl)methyl] propanamide (66), prepared as shown below, to nitrating conditions [trifluoro acetic acid (TFA-HNO_3)]. This product may well prove to be an important intermediate en route to ergot alkaloids.



(62) (63) (64) (65) (66)

(66)


HNO3 - TFA
HNCOEt
NO2
MeO
NHCOEt
O2N
MeO
(67)
+
NHCOEt
MeO
NO2
(68)
EtCON
NO2
MeO
(69)
- TFA
EtCON
NO2
O

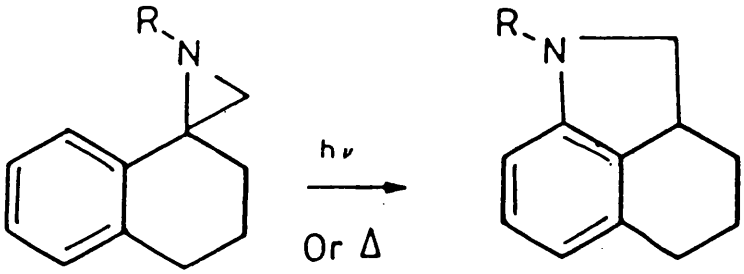
(70)

CHAPTER ONE

2.1.1 INTRODUCTION

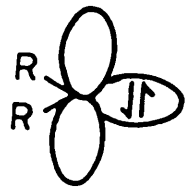
2.1.1.1 Imines as intermediates in aziridine synthesis

In this research programme a new synthetic route to the ergoline system was considered. This involved the preparation of an aziridine intermediate, e.g. (71), which might then be fragmented photochemically or thermally to afford a diradical species (or its equivalent) which could recyclise to give the basic structural unit (72) of the ergotamines. Additionally, the possibility of concerted 1,3-sigmatropic rearrangement of (71) to (72) was anticipated.

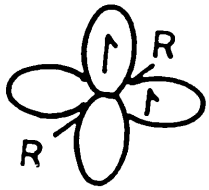


(71) (72)

Many classical routes to aziridines make use of the carbene addition to imines and it was decided that this approach could be applied to give structure (71).



(73)



(74)

The simplest carbene, $:CH_2$, is usually called carbene, or more correctly methylene, and the structure :CHCl is called monochlorocarbene or chloro-methylene, and so on.

The relative energies of the different possible structures determine the chemical behaviour of carbenes. Although there is no obvious way of predicting the ground state of carbenes, e.g. the ground state of methylene, probably approximates to a structure such as (74; R=H), whereas that of difluorocarbene is best represented by the singlet structure (73; R=H). There are two approaches to the problem; direct detection of the ground state and the excited states by spectroscopic means, and molecular orbital calculations.

Carbenes can be generated by a concerted elimination, or <u>via</u> carbanion, radical or carbonium ion intermediates. Carbanion and radical react by some pathway that does not involve carbenes, but their structural features allow carbenes to be generated by them. These features, however, are not found in carbonium ions.

2.1.1.2 Some examples of reactions generally used to form carbenes are:

2.1.1.2.1 From diazoalkenes

The photolysis or thermolysis of diazoalkenes give a very common route to the generation of carbenes. Diazomethane, for example, decomposes to yield methylene, $:CH_2$, as an intermediate which was first reported by Nef

$$CH_2N_2 \xrightarrow[\Delta]{h\nu} :CH_2 + N_2$$

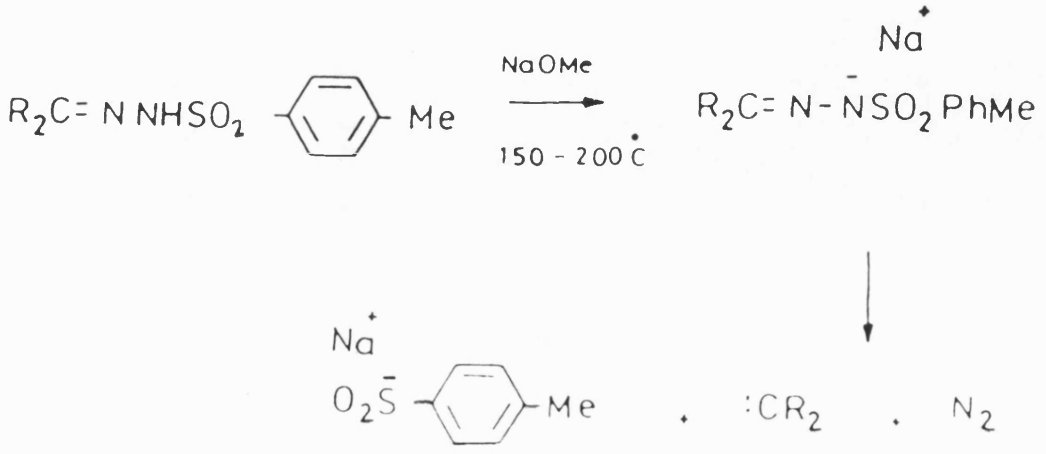
2.1.1.2.2 From hydrazones:

Hydrazones can be oxidised to diazoalkanes in mild conditions, using mercuric oxide, silver oxide or lead tetra-acetate.

$$R_2C=N-NH_2 \xrightarrow{HgO} R_2C=N_2 \longrightarrow R_2C: + N_2$$

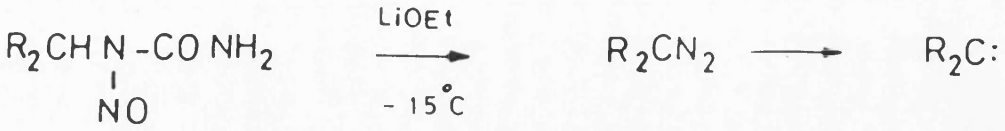
2.1.1.2.3 From toluene -p-sulphonylhydrazones

The toluene -p-sulphonylhydrazones are converted into their sodium or lithium salts, which are then pyrolysed or photolysed to give carbenes. These carbenes are generated directly i.e. salts of toluene-p-sulphonylhydrazones are not isolated.



2.1.1.2.4 From N-nitrosoalkylureas:

The reaction of N-nitrosoalkylureas with bases is another known route to diazoalkenes which in turn generate carbenes.



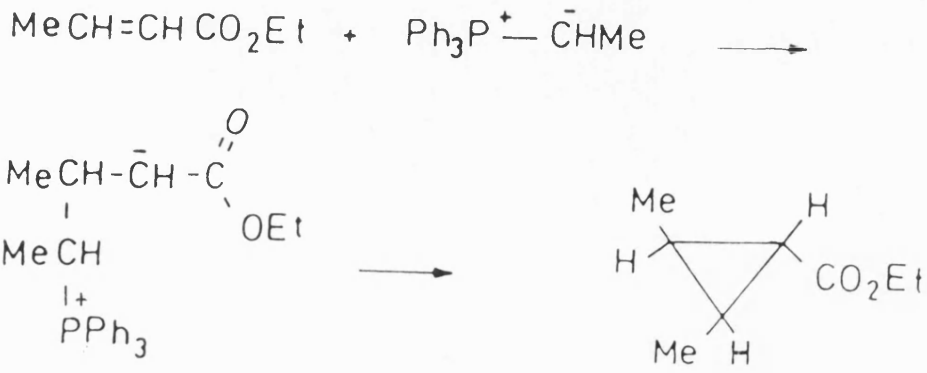
2.1.1.2.5 From ketenes:

Like diazoalkenes, ketenes are also a source of carbenes, since the reaction involves the loss of a stable molecule, carbon monoxide:

However, this procedure was reported not to be a good one, as the ketenes tend to polymerise in the conditions needed to generate the carbene.

2.1.1.2.6 From ylides:

Sulphur, phosphorus and nitrogen ylides can react with alkenes to give cyclopropanes, but carbenes are not usually intermediates. The ylides act as nucleophiles, attacking an electrophilic double bond in a two step process.



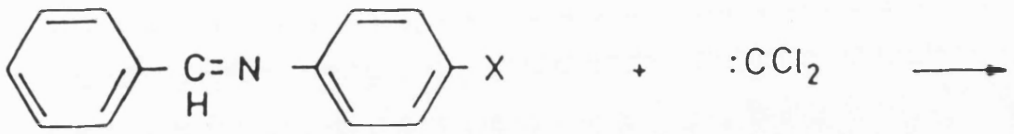
2.1.1.2.7 From carbanions:

The modern carbene chemistry was known since the 1950's with the elucidation of the mechanism of the basic hydrolysis of chloroform by J. Hine and his co-workers[85]. They showed that the trichloromethyl anion and dichlorocarbene were both intermediates in the reaction, the carbene being formed from the carbanions in the rate determining step:

$$\bar{C}Cl_3 \longrightarrow :CCl_2 + Cl^-$$

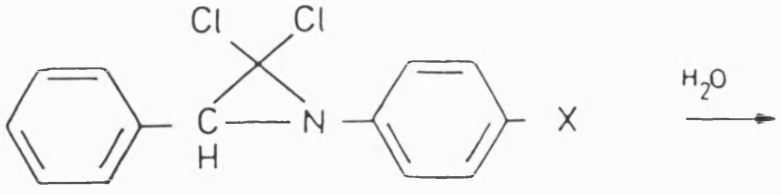
Evidence on which this conclusion is based is as follows. In deuterated solvents, the basic hydrolysis of chloroform is slow compared with the rate of incorporation of deuterium into the chloroform, so there must be a rapid pre-equilibrium in the hydrolysis by hydroxide ions:

$$CHCl_3 + \bar{O}H \rightleftharpoons \bar{C}Cl_3 + H_2O$$



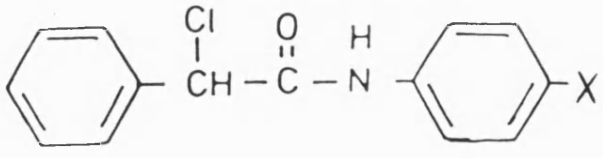
(75) X = -Cl

(76) X = $-OC_2H_5$



(77) X = -Cl

(78) X = $-OC_2H_5$



(79)

Scheme (11)

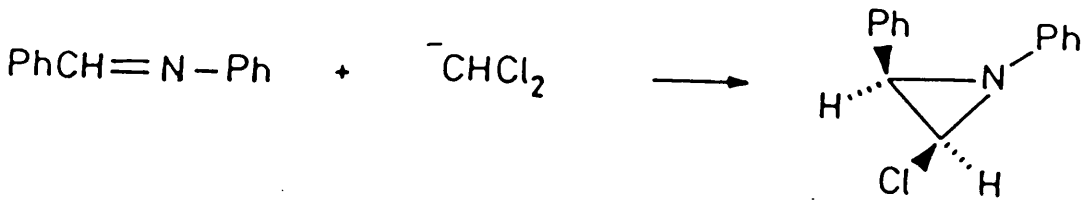
2.1.1.3 Reactions of carbenes with imines:

As reported by Kadaba and Edwards[33] the presence of an electron-withdrawing group on the N-phenyl group has a large polar effect on the imine and hence its reactivity towards nucleophiles. At the same time the carbon of the carbon-nitrogen double bond will be less susceptible to electrophiles. In the following year (1962) a report by Cook and Fields[34] on the reaction of benzylidene-p-chloroaniline (75) with dichlorocarbene generated in situ from potassium t-butoxide and chloroform resulted in a 68% yield of 1-p-chlorophenyl-3-phenyl-2,2-dichloroaziridine (77). Similarly dichlorocarbene was added to N-benzylidene-p-phenetidine (76) to produce 1-p-ethoxyphenyl-3-phenyl-2,2-dichloroaziridine (78) in 91% yield.

The hydrolysis of these compounds formed the corresponding α-chloro-α-phenylacetanilides (79), and in quantitative yields. See Scheme 11.

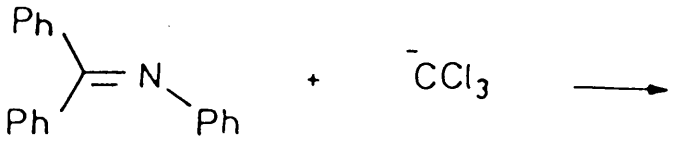
In 1965 Deyrup and Greenwald[35,36] reported the synthesis of monochloroaziridines and their use. They used, a stable reagent, $LiCHCl_2$, prepared previously by Kobrich from butyllithium and methylene chloride at -110°C. N-benzylideneaniline in ether was added at temperatures below -70°C. A homogeneous orange solution was produced and allowed to warm up to room temperature. The authors reported a high yield of crude product. However, the monochloroaziridine was too reactive to allow purification for analysis; hence the structure was supported by spectral data as well as by conversion to suitable derivatives.

Inspection of the ^1H n.m.r. spectrum of this material revealed two doublets centred at 3.12 and 4.33ppm (in addition to complex phenyl absorption). The absence of other absorptions which could possibly be attributed to the other isomer indicated the exclusive course of the reaction and the magnitude of the coupling constant (as well as other evidence) demonstrates that this reaction stereoselectively yields the cis-isomer (80).

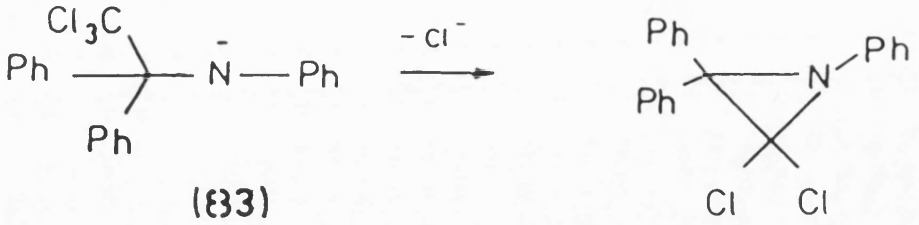


(80)

Deyrup and Greenwald then investigated the possibility of the anion (81), shown in Scheme 12, to act as an intermediate in the conversion of the imine (82) to the dichloroaziridine (84). The sequence then being the reaction of the base with chloroform to yield the species (81) which then added to the carbon atom of the imine. The derived anion (83) then cyclises with loss of chloride.



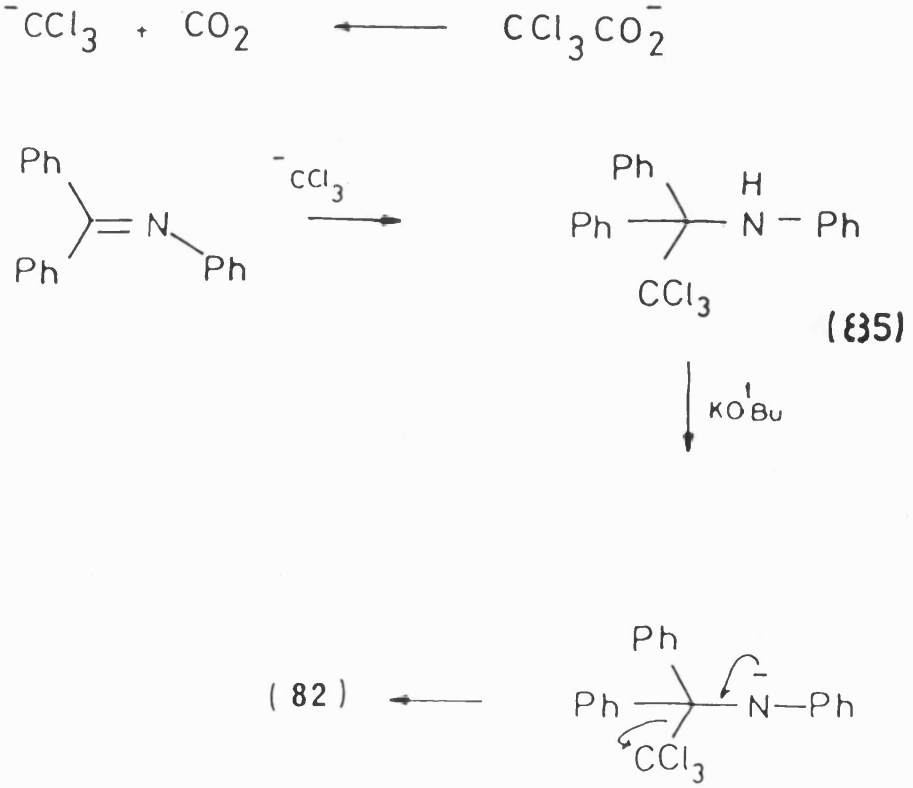
(82) (81)



(83) (84)

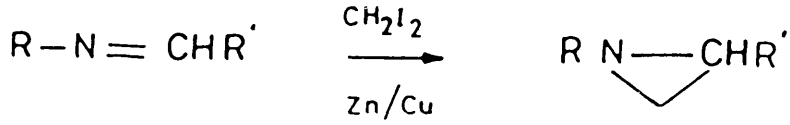
Scheme (12)

However, when the anion (83) was prepared in a different way, i.e. by adding trichloroacetic acid to the imine, to yield (85) followed by base treatment no detectable dichloroaziridine was produced as shown in scheme 13. Thus it was concluded that free dichlorocarbene was required to be generated by the loss of a chloride ion from the trichloromethyl anion. This then added to the imine directly.

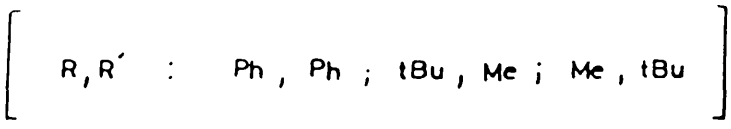


Scheme (13)

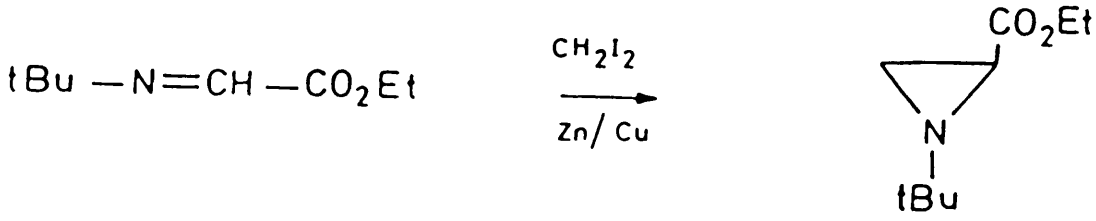
In 1972 Baret and Pierre[37,40] applied the Simmons-Smith[38,39] reaction to some imines. They found that the reaction did not take place with imines containing electron-releasing groups on both the carbon and the nitrogen atoms of the imine unit. However, with the α-imino ester (86) the aziridine (87) was formed in 40% yield.



$$R-N=CHR' \xrightarrow[Zn/Cu]{CH_2I_2} R\,N\!-\!CHR'$$



$$[\ R,R' : Ph, Ph\ ;\ tBu, Me\ ;\ Me, tBu\ ]$$

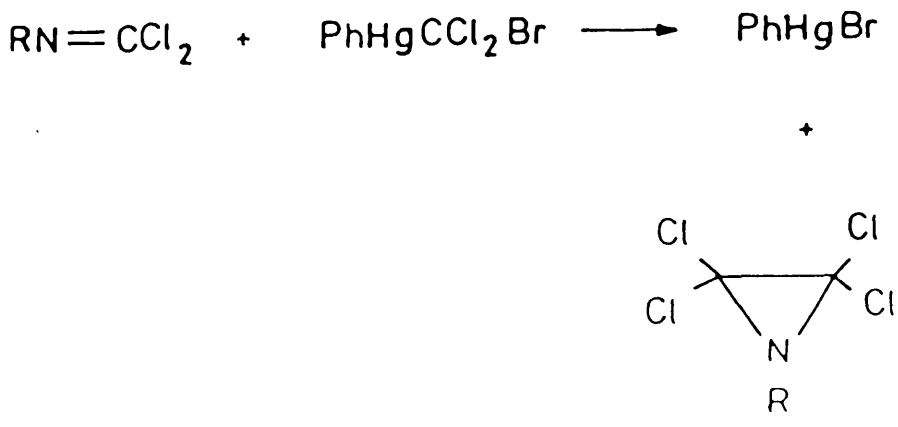


$$tBu-N=CH-CO_2Et \xrightarrow[Zn/Cu]{CH_2I_2}$$

(86)

(87)

Seyferth[41] used phenyl(bromodichloromethyl) mercury to transfer CCl_2 to alkyl and aryl carbonimidoyl dichlorides to give 1-aryl-2,2,3,3-tetrachloroaziridines in fair yields. These C-tetrachloroaziridines are much more stable thermally than the corresponding monochloro- or gem-dichloroaziridines, but they do rearrange to give acyclic molecules of the type $RN=C(Cl)-CCl_3$ when heated at 180°C for some hours.



$$RN=CCl_2 + PhHgCCl_2Br \longrightarrow PhHgBr +$$

In order to achieve successful carbene addition to imines via phenyl(trihalomethyl) mercury reagents, one must decrease the nucleophilicity of the nitrogen atom. The carboniminidoyl dihalides $RN{=}CX_2$, are such a class of imines in which nitrogen atom of the C=N is less nucleophilic as a result of the electron-withdrawing effect of the two halogen substituents on the carbon atom of the C=N bond. This decrease in the availability of the lone pair on nitrogen is sufficient to allow successful CX_2 extrusion from $PhHgCX_2Br$ and subsequent CX_2 addition to C=N bonds.

2.1.2 DISCUSSION

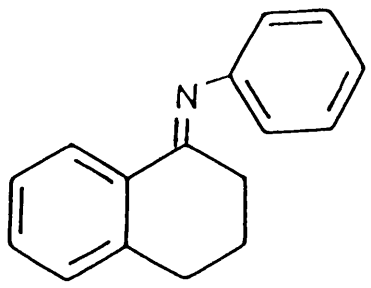
2.1.2.1 Synthesis and some aspects of the Chemistry of the 1,2,3,4-tetrahydro-1-(N-phenylimino)-naphthalene

As previously discussed the intention was to prepare the aziridine (71) and some related structures, and to examine its thermal and photochemical behaviour. The primary objective was the imine (88) which should afford the required aziridine through the addition of carbene.

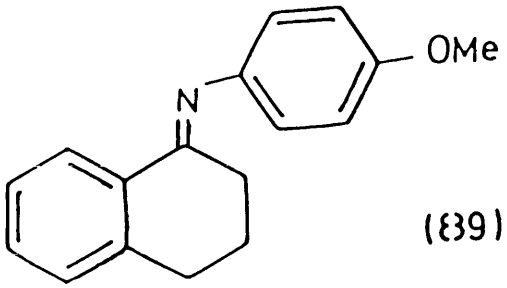
The Schiff's base or anil (88) was first prepared by Bogdanowicz-Szwed[42] in 1977 by the condensation of α-tetralone with aniline in boiling xylene with a trace of p-toluenesulphonic acid. In this case a solvent like benzene with a lower boiling point was used. However, this gave a lower yield of 63% than the reported 84%. The yield was then increased to 80% when the ion exchange resin Amberlyst R-15 (strongly acidic), see page 10, was used instead of p-toluene sulphonic acid. The use of a resin catalyst has therefore, the advantage of keeping a low reaction temperature and gaining a higher yield.

In this research programme many attempts were made to use the anil (88) and its reactions with carbenes in the preparation of aziridines. The formation of these aziridines, which will be described in chapter three, is required in order to investigate a potential new synthetic pathway to the ergoline system. Although this objective has not been realised a range of new reactions has been uncovered.

In this chapter the attempted addition reactions of carbenes to the anil (88) will be discussed. These carbenes were reacted with this anil and the 4'-methoxy derivative (89). Compound (89) was synthesised in a similar fashion to (88), and it was anticipated that the extra electron density created on the nitrogen atom by the methoxy substituent should increase the rate at which electron deficient species, such as carbenes, would react with it.



(88)



(89)

The stereochemistry of (88) is almost certainly that shown but no effort has been made to establish it as such.

The stability of this compound is accounted for by the extensive conjugation from the N-phenylimino group through to the fused aromatic ring. This conjugation will have an effect on the various reactions of (88) as described later.

The other factor which plays a role in the behaviour of (88) is the imine-enamine relationship and although (88) is capable of tautomerism with the enamine form of 88', the equilibrium both in the solid phase (infra-red spectroscopy) and in solution (^{1}H, C^{13} n.m.r.) is not detected and only the imine tautomer is present.

Again this must be due to the extended conjugation of the imine.
By comparison the enamine is cross conjugated but as we shall see, the chemical reactions of this anil are clearly influenced by the potential tautomeric behaviour.

Initially it was observed no reaction with either anils utilizing carbenoids generated by the Simmons-Smith procedure[38] or through the thermolysis or photolysis of diazomethane. In all these reactions the starting anil was returned unchanged. Similarly, nothing happened when ethyldiazoacetate and rhodium acetate were reacted with the parent imine (88) at 130°C in chlorobenzene or at 155°C in dichlorobenzene. These reactions were repeated several times but no addition took place.

However, when the imine (88) and ethyl diazoacetate were irradiated together in dry benzene using a Hanovia low pressure (16W) ultra-violet lamp, two isomeric products were formed in 2:1 ratio. The two isomers were separated by repeated column chromatography, and it was discovered that these compounds which had the molecular formula $C_{30}H_{21}NO_2$ exhibited different carbonyl frequencies in their infrared spectra. These bands were at ν_{max} 1770 and 1750cm^{-1} respectively. The difference in these frequencies was puzzling and at first it was thought that two very different structures were involved.

The ^1H n.m.r. spectra were similar and also familiar, for apart from chemical shift differences the patterns of the aromatic and methylene proton resonances of the parent imine were more or less the same as those of the new structures. In addition, each new spectrum gave rise to a low field methine singlet and an A_3X_2 five proton spin-spin system consistent

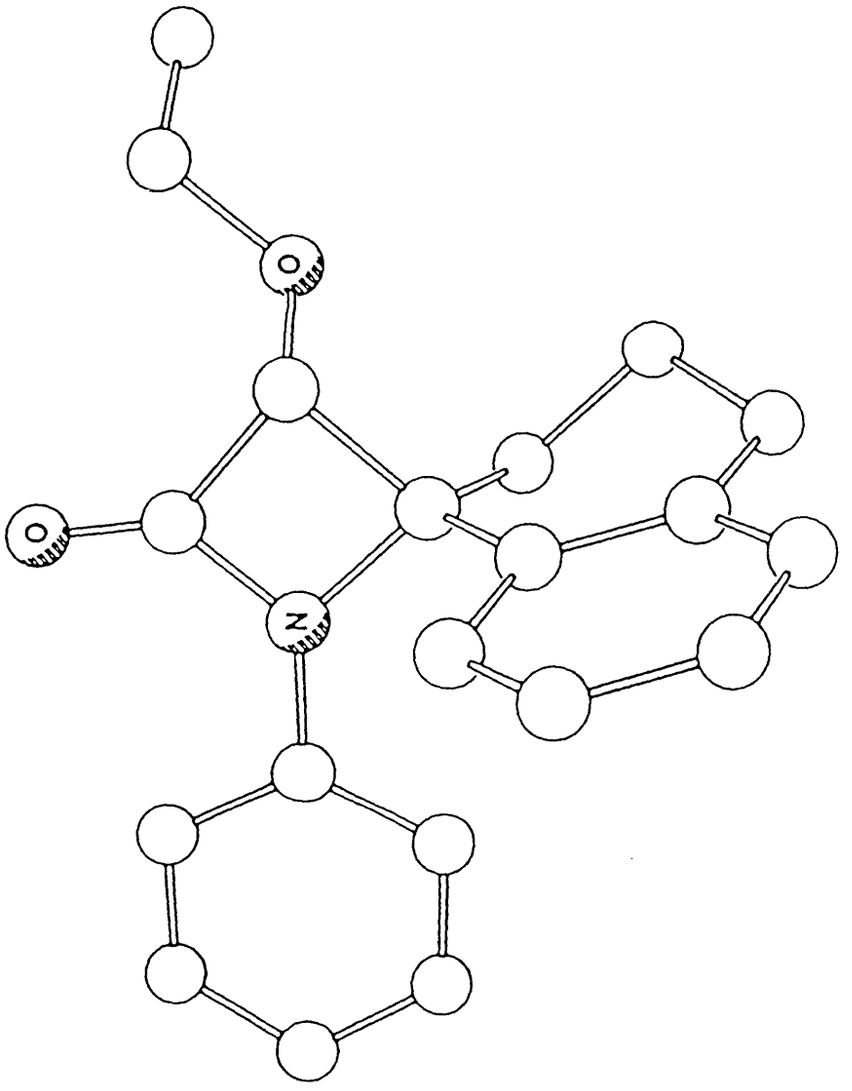


Fig. 1

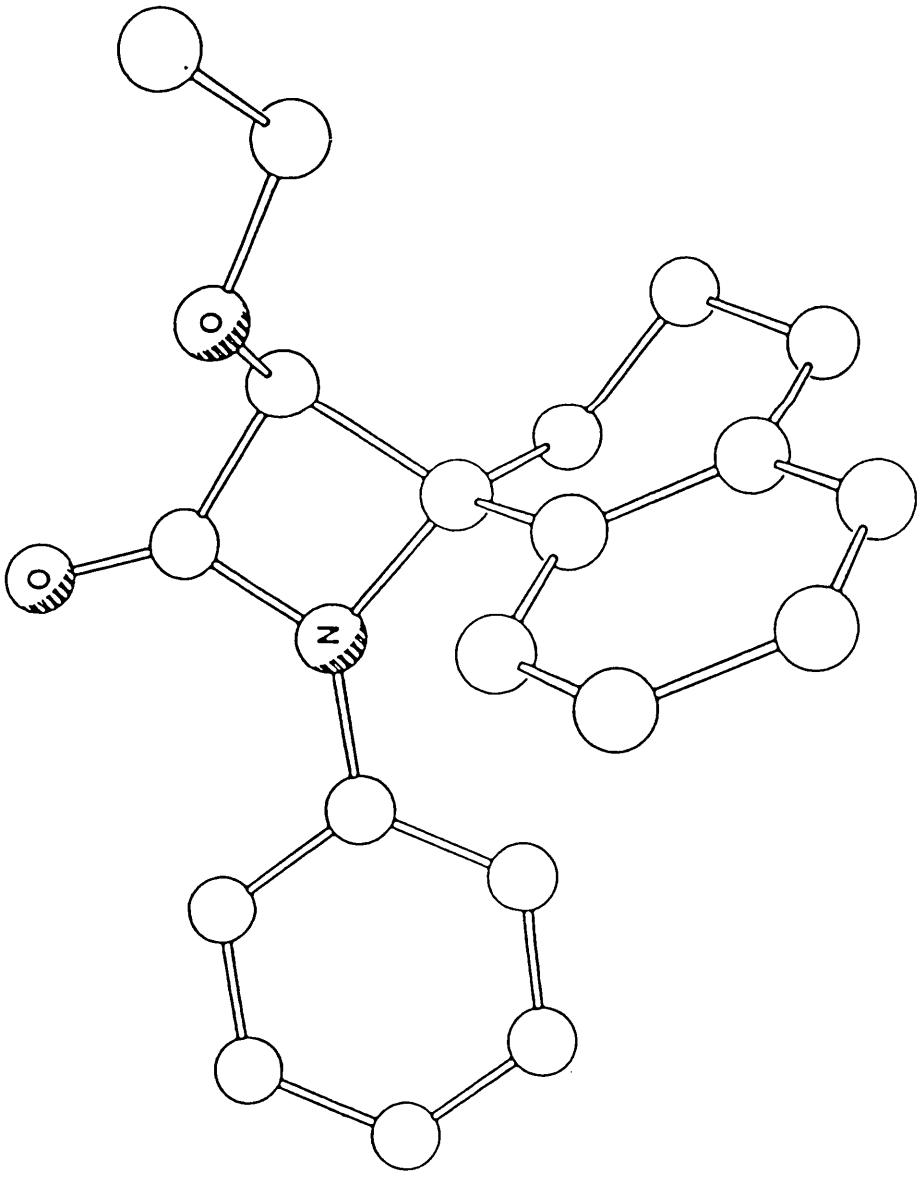
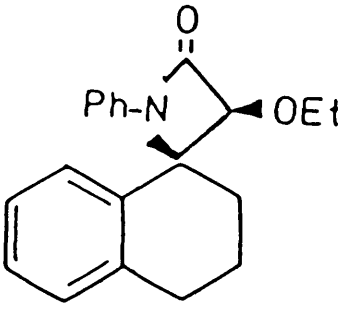


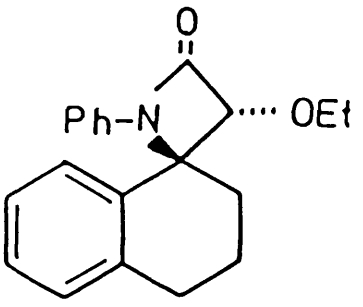
Fig. 2

with the resonances of an ethoxy group. From this and other data it was considered that the two β-lactam structures (90) and (91) had formed. This conclusion and structural assignments for the individual products were finally obtained by X-ray analysis of single crystals, see Figs. 1 and 2.



cis

(90)



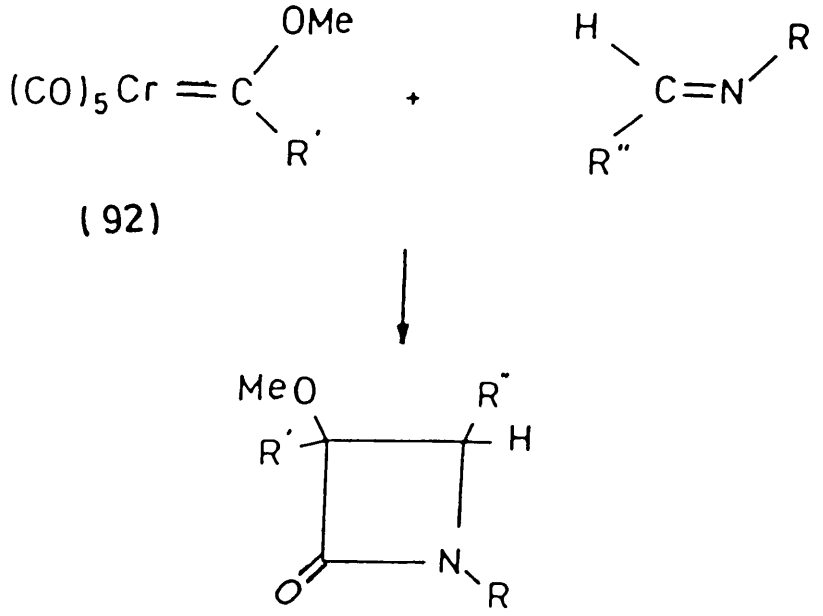
trans

(91)

As explained previously a difference in the infra-red spectra of the two β-lactam isomers existed. These spectra were recorded using a Nujol mull. The carbonyl absorption bands appeared at $\nu_{max}1770cm^{-1}$ for the β-isomer (90) and at $\nu_{max}1750cm^{-1}$ for the α-isomer (91) but, when a solution of either isomers in chloroform was used to record their infra-red spectra each isomer gave a carbonyl absorption at $\nu_{max}1750cm^{-1}$. One hypothesis

which could explain this phenomena was probably due to packing and associated effects of the solid state. Unfortunately no other data was available to support this hyopthesis.

Various authors[112] have shown that when imines are irradiated with ultra-violet light in the presence of pentacarbonyl chromium complexes (92), β-lactams are formed in good yield.



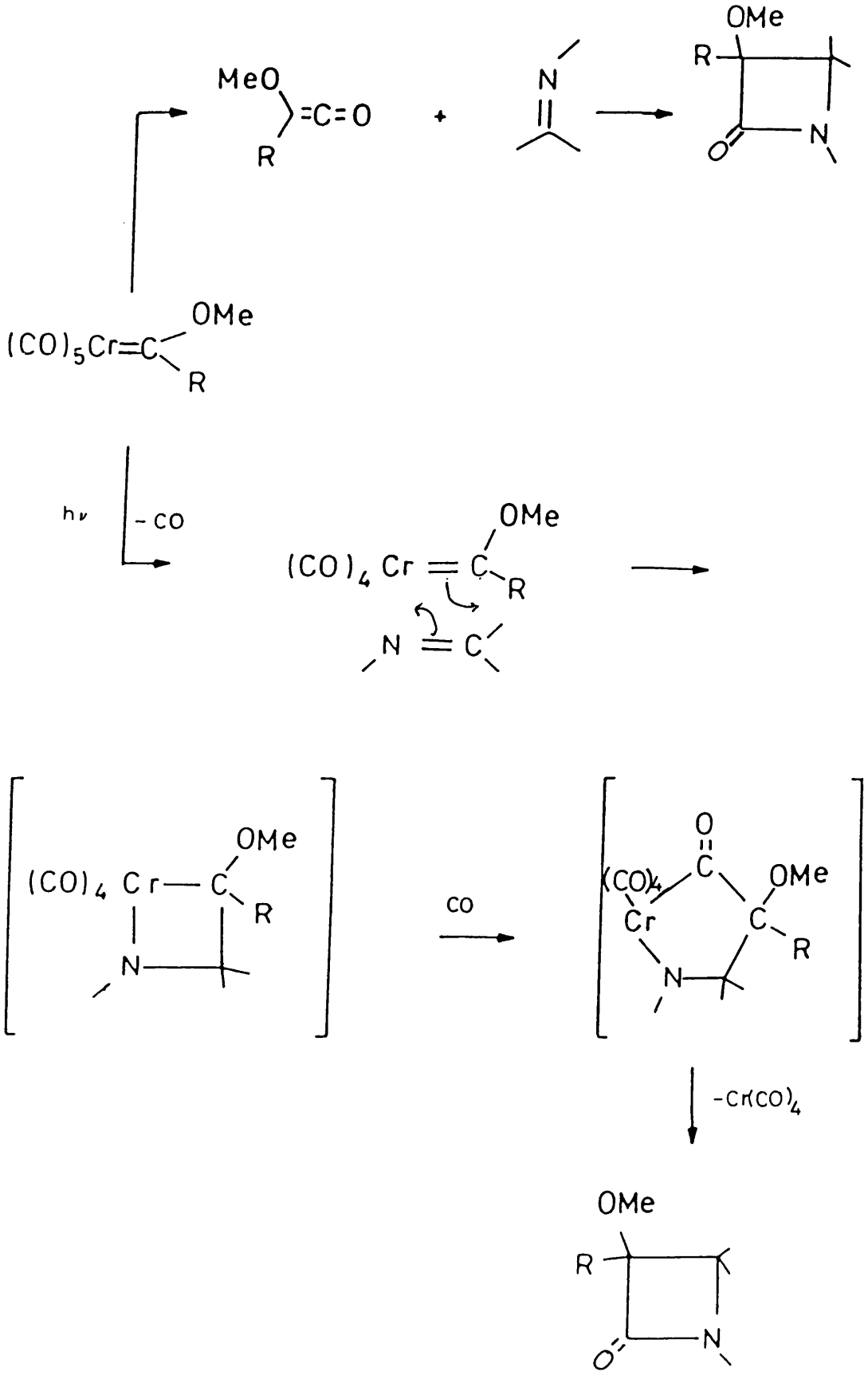
(92)

(93) $R' = R = Me, R'', Ph$

(94) $R' = Me, R'' = R = Ph$

(95) $R' = R'' = Ph, R = Me$

Scheme (14)


MeO
R
=C=O
+
N
OMe
R
O
N
(CO)5Cr=C
OMe
R
hν
-CO
(CO)4 Cr = C
OMe
R
N = C
(CO)4 Cr — C
OMe
R
N
CO
(CO)4
Cr
O
C
OMe
C
R
N
-Cr(CO)4
OMe
R
O
N

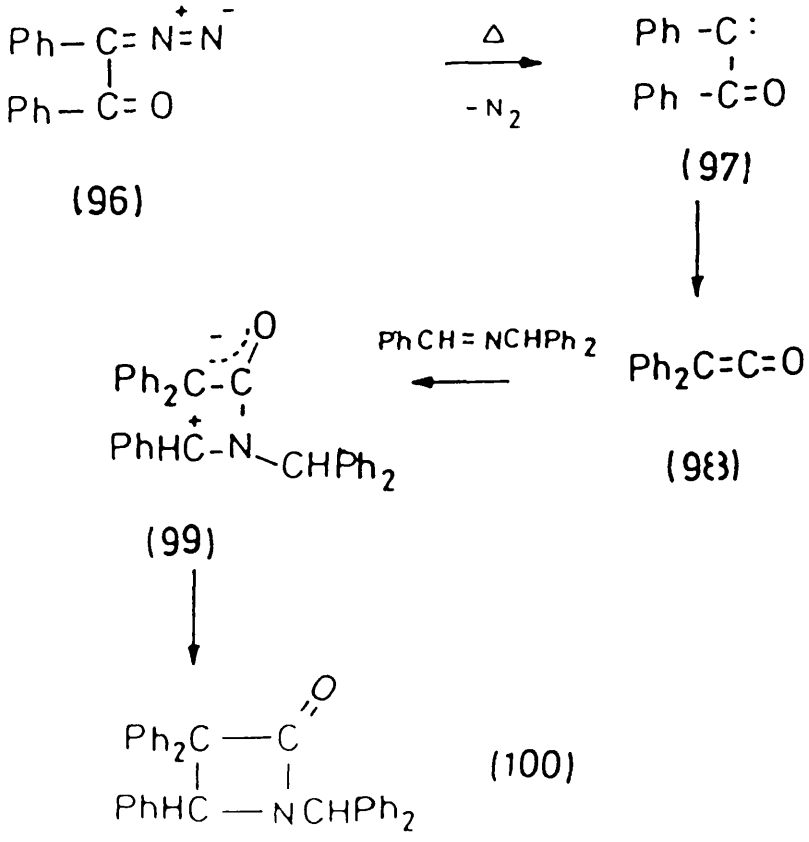
The mechanism of such reactions was explained in two ways; either,

(a) A ketene was produced which then added to the imine, or

(b) A cycloaddition took place between the imine and the species (93-95) formed from the complex by loss of CO. After the addition further loss of CO to give a structure which eliminated chromium and more CO to give the product, see Scheme 14.

Mehrotra and Singh[43] suggest that the formation of the β-lactam (100) through the thermolysis of azabenzil (96) and N-benzylhydrylimine takes the following course:

Firstly nitrogen was lost from the aza compound to yield the carbene (97) which then underwent Wolff rearrangement to the ketene (98). This species added to the imine, but since a concerted (2+2) π <u>syn</u>- addition was disfavoured in a thermal process the reaction proceeded in a step-wise fashion <u>via</u> the Zwitterion (99) as seen below.



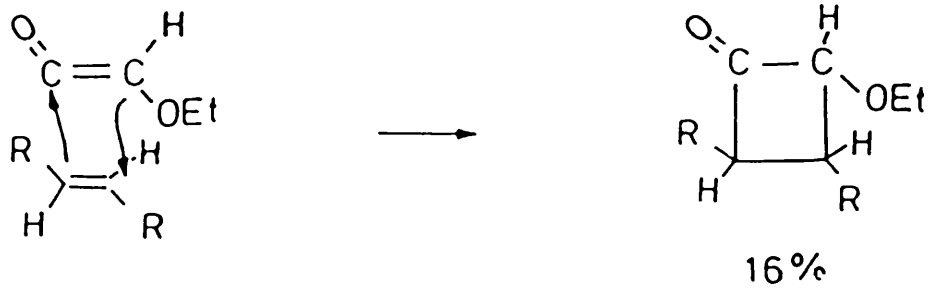
(96) (97) (98) (99) (100)

Ethyl diazoacetate on photolysis, similarly afforded the ketene form . DoMinh and Strausz[44] have shown that this species add to both cis and trans alkenes in such a way that a three fold isomeric relationship was set up:

(i) the geometrical configuration of the parent alkene was maintained,

(ii) the orientation of the ethoxy group is always syn to an adjacent alkyl group in the product rather than to a hydrogen atom, thus an anti arrangement is never observed,

(iii) with unsymmetrical alkenes only cycloadducts having a substituent in a position vicinal to the ethoxy group are formed (head-head) addition.



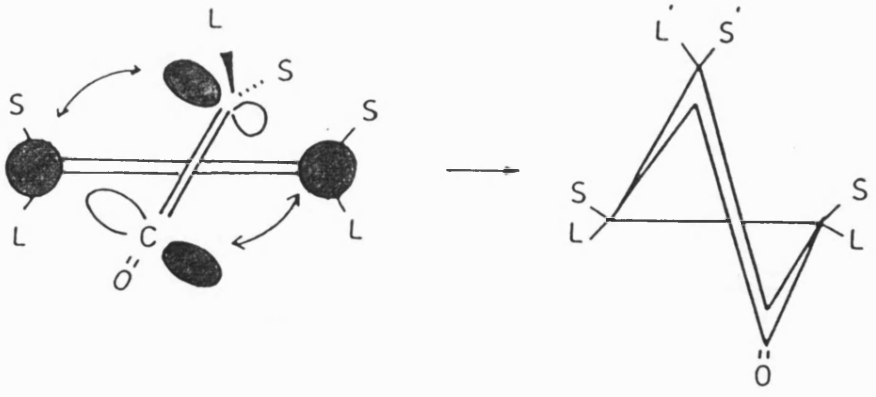
16%

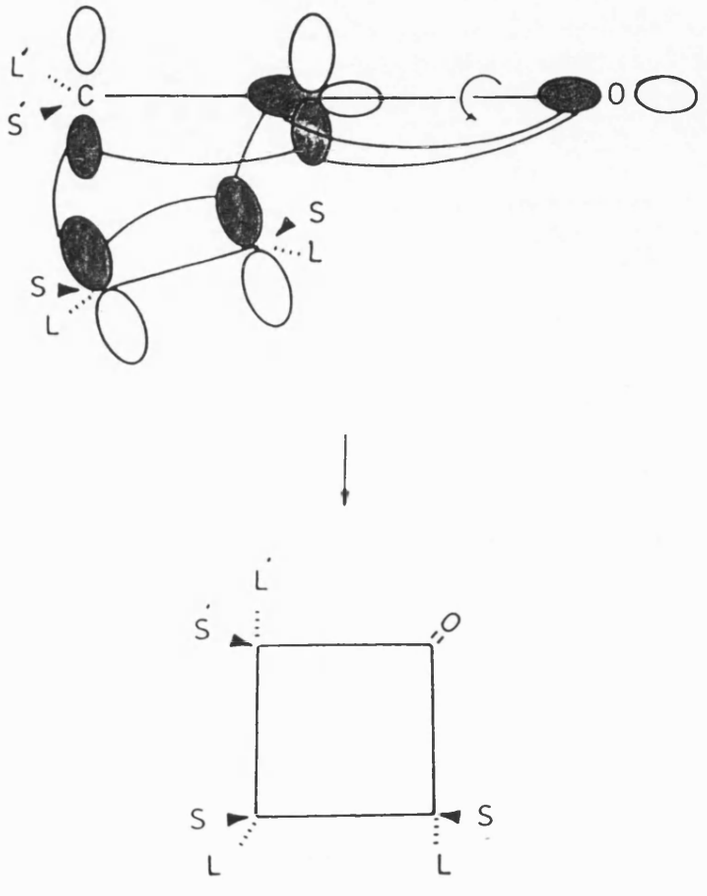
These results suggest a high degree of order and preference in the transition state which is not obvious in species like Mehrotra and Singh's Zwitterionic intermediate (99).

Woodward and Hoffman considered ketenes to behave as vinyluim ylides (102) and as such may add to π-systems in an antrafacial manner under thermal conditions, i.e. in a concerted, and hence a highly ordered $[\pi_s^2 + \pi_a^2]$ cycloaddition.

(101) (102)

The place of the vacant p orbital of the simply vinylium[45] ion is thus taken up by the unoccupied $\pi^*_{C=O}$ orbital of the ketene, and the high electrophilic reactivity of ketenes is a consequence of the exceptionally low lying nature of the orbital. Thus as the reactants approach one another at right angles there is a good HOMO/LUMO interaction of the π-electrons of the alkene (HOMO) with this antibonding orbital on the ketene (LUMO).





Scheme (15)

An alternative geometry of approach has been proposed for the alkene-ketene addition. One end of the alkene double bond interacts with the ketene c=c π bond but the other end interacts with the carbon end of the perpendicular c=oπ bond. This is due to the two p orbitals on the central sp-hybridised carbon are orthogonal, it is necessary to postulate that in the transition state the oxygen p orbital that forms the other end of the c=o π bond will rotate so as to overlap both of the sp carbon's p orbitals and will thus establish the pericyclic path or orbitals. Since the carbonyl π bond is part of the pericyclic path according to this proposal, the reaction is $\pi 2S+\pi 2S+\pi 2S$. There are six electrons and zero phase inversion, so the process is allowed[96]. See Scheme 15.

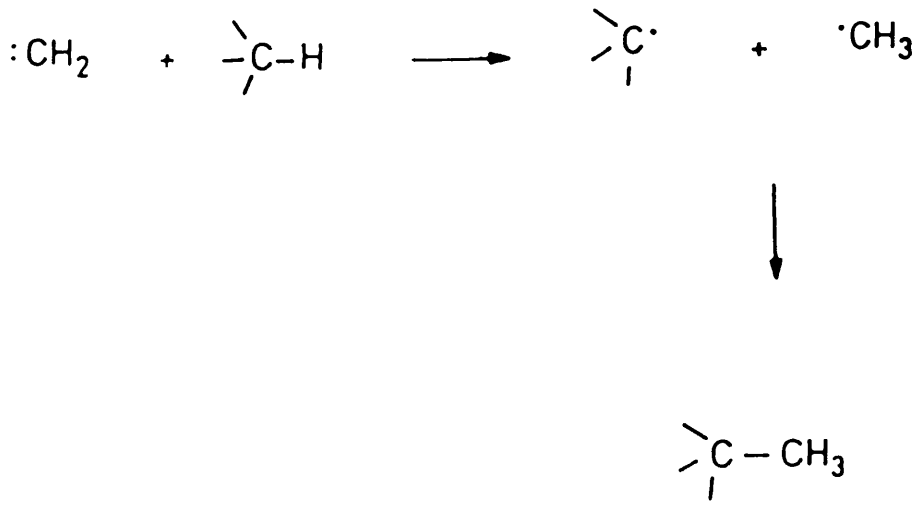
In the build up to the transition state steric repulsion would prevent the approach of the alkene on the same side as the ethoxy group, moreover, the approach is sterically more favourable if the bulky substituent on the alkene points away from the ketene. These factors then account for the preference observed in the formation of the <u>syn</u>-cycloadduct.

In the present example the β-stereoisomer was isolated in approximately twice the amount of the α-isomer. As the ratio of the products present in the reaction mixture itself was not monitored it was not possible to make a firm statement about these results (i.e., quoted was an isolated product yield not an actual value).

The two spiro β-lactams proved to be very stable towards heat, aqueous alkali and hydrogen chloride in methanol, and this was something of a disappointment since it was hoped that ring opening of the lactam ring might afford useful intermediates en route to the ultimate targets.

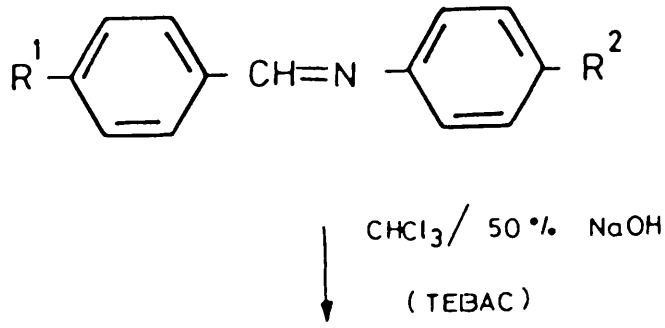
Mehrotra and Singh also found their β-lactam to be quite stable and it remained unchanged on heating to reflux for 30 hours with either conc. hydrochloric acid or 40% aq. alkali (NaOH or KOH) or ethanolic potassium hydroxide. This β-lactam was also unaffected on treatment with either lithium aluminium hydride or phenylmagnesium bromide.

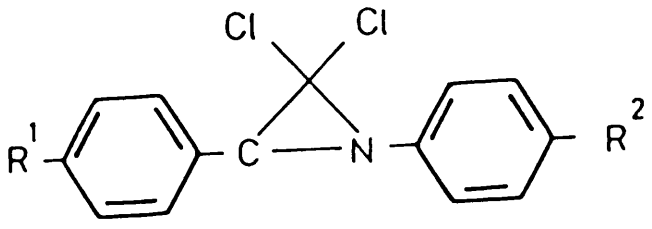
Earlier it was described how the attempted reactions of carbene itself with the imines (88 and 89) had failed. Carbene is normally regarded to exist in the triplet state and hence it reacts in a rather different manner to the unselective singlet state which is formed initially.
When a carbene is in the triplet state, a hydrogen abstraction to yield a radical pair seems a reasonable possibility for the insertion mechanisms into methine system. This therefore explains the slow reactivity of a carbene in its triplet state[46,47,48,49].



Dichlorocarbene is produced in the singlet form since back donation from the lone pair of electrons on the chlorine atoms is assumed to stabilise the formally vacant orbital on carbon. However, when the imine (88) was reacted with this species, generated in situ by treatment of chloroform with potassium t-butoxide, or with sodium methoxide, no products were found and the starting material remained unchanged at the end of the reaction.

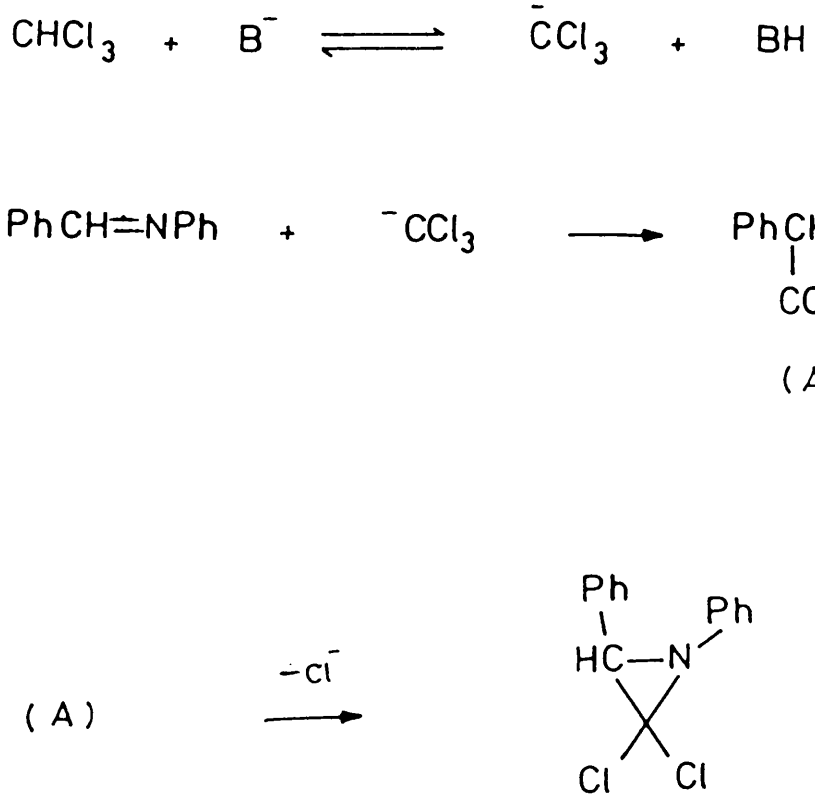
This is in opposition to other experience, for Graefe[50] showed that benzylideneanilines react with chloroform in 50% aq. sodium hydroxide in the presence of the phase transfer catalyst triethylbenzylammonium chloride (TEBAC) to give the aziridine, as shown below:





88 %

Similar results have been reported by Sandri[51] and by Makosza.[52] The last author suggested that the reaction in aqueous media might not involve dichlorocarbene at all. Thus it was proposed that the trichloromethyl anion added to the electron deficient carbon atom of imines, yielding the anion (A) which ring-closed by intramolecular elimination of chloride ion.



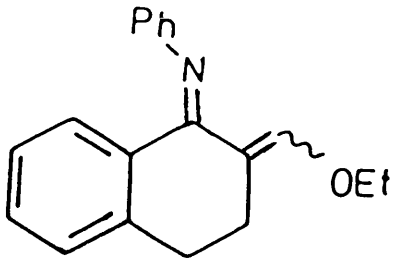
This type of mechanism was favoured because of the ionic environment provided by the aqueous conditions and the transfer catalyst, but unfortunately when the reaction was applied to the imines (88 or 89) no aziridine products were obtained.

The reason for this failure was not obvious in the view of the success of the previous workers, especially since their substrates were closely related to (88). However,the cause will be unravelled in later discussion.

Clearly, disregarding steric effects substituents in the aryl ring which would increase the electrophilicity of the carbon atom of the imine and simultaneously help delocalise the negative charge on the nitrogen atom of the transition state would favour aziridine formation. This work was discontinued since Regen and Singh[53] presented a very convenient procedure for the generation of dichlorocarbene through the reaction of solid (dry) sodium hydroxide with chloroform, "homogenation" being achieved through ultrasonic irradiation.

These conditions were used in a reaction with the anil (88) but instead of the expected aziridine a crystalline compound was obtained which did not contain chlorine atoms. Instead the molecular ion peak was observed at m/z 277 consistent with the molecular formula $C_{19}H_{19}NO$. From an analysis of the ^1H n.m.r. spectrum the presence of an ethoxy group was discerned. In addition there was an extra resonance in the aromatic/olefinic region compared to the parent imine. At 100MHz this part of the spectrum was very well resolved and the individual signals of the tetrahydronaphthalene unit were easily identified. However there were four methylene resonances rather than the six of the parent imine. One pair of these methylene protons resonated as a triplet at δ2.6 (J=7Hz) commensurate with benzylic protons at C-4 of a tetrahydronaphthalene system, but the other pair formed

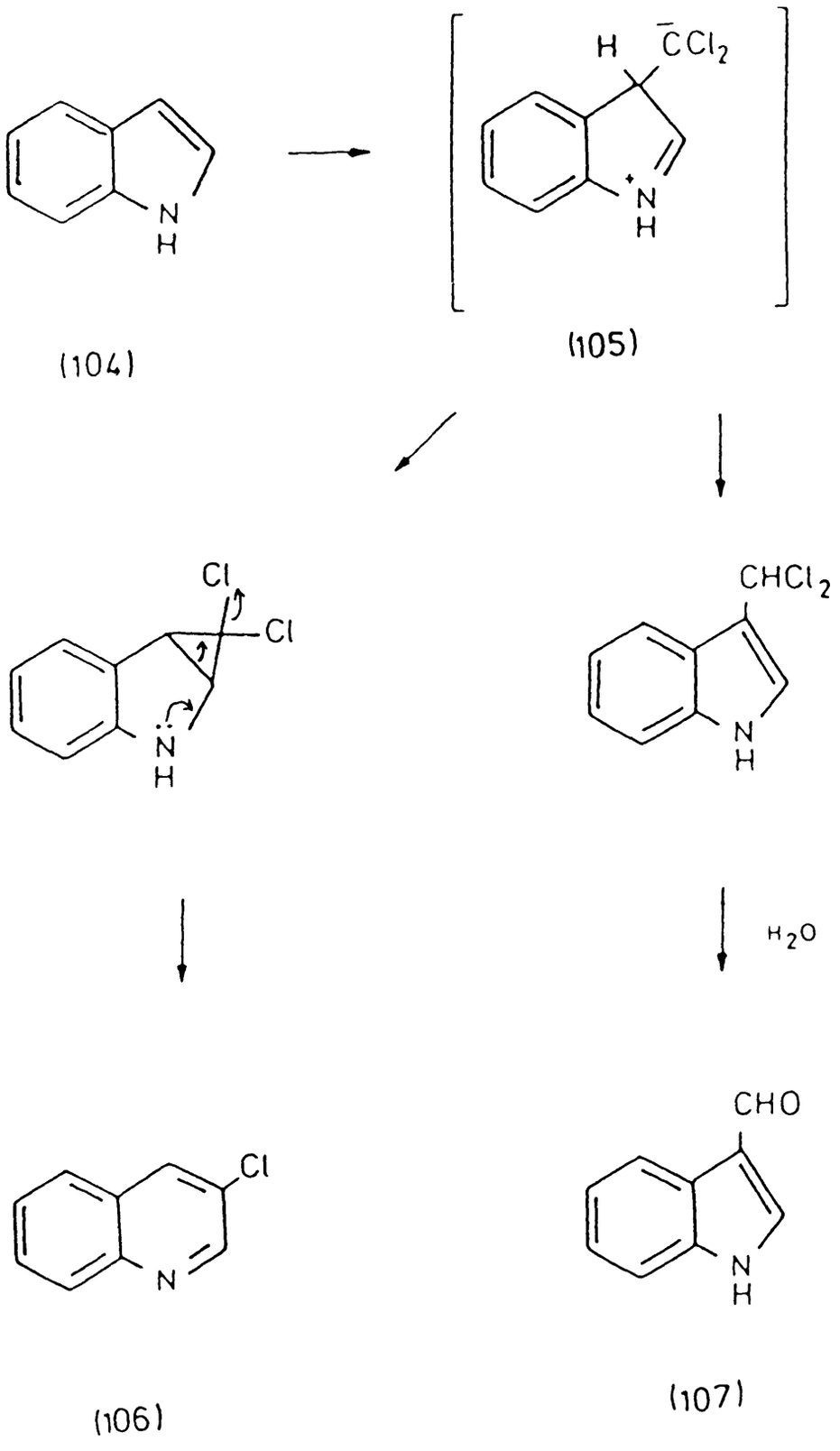
a triplet of doublets at δ2.15 (J_1=7Hz; J_2=5Hz). These data were best accommodated by structure (103) although the stereochemistry still remains uncertain.



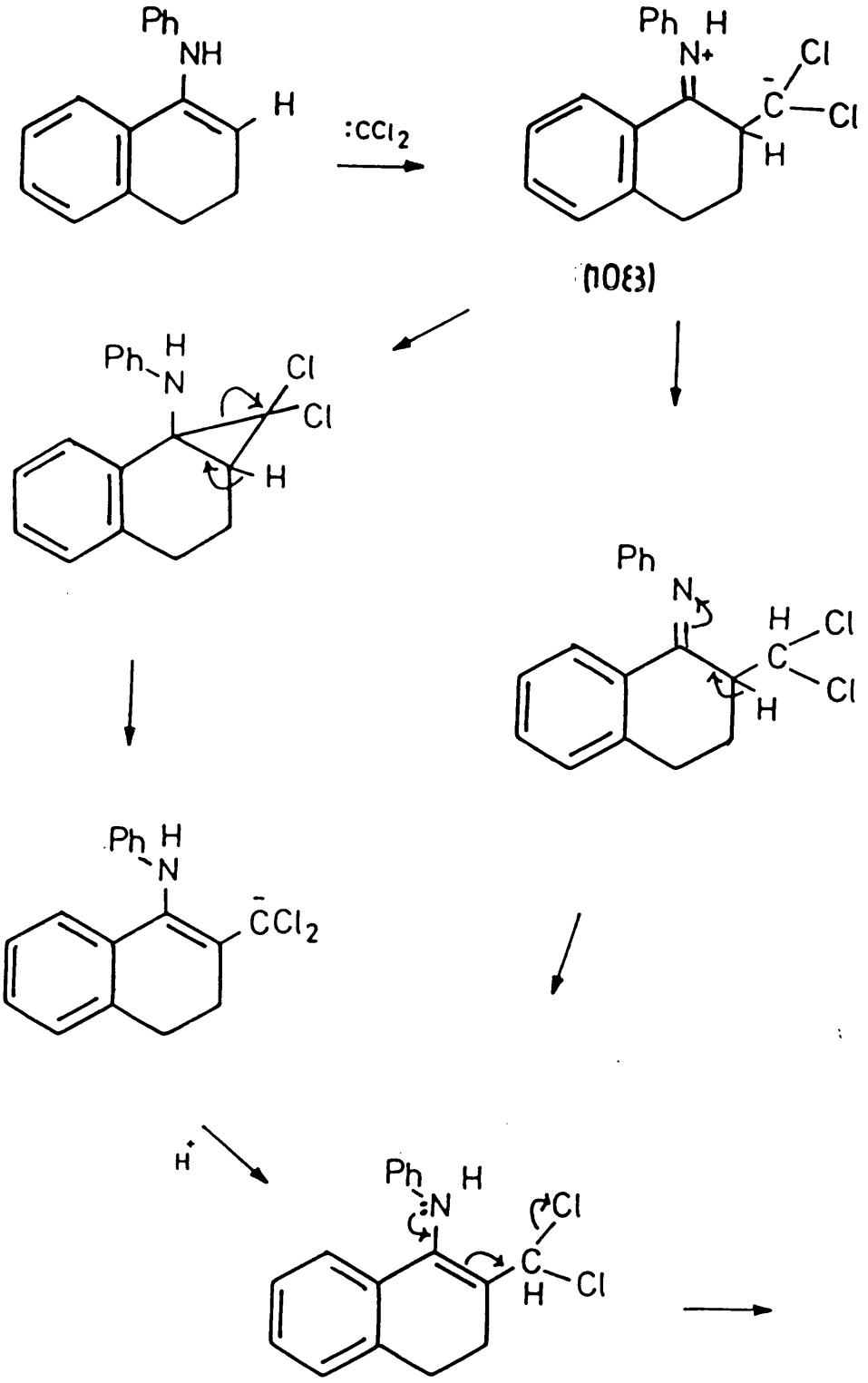
(103)

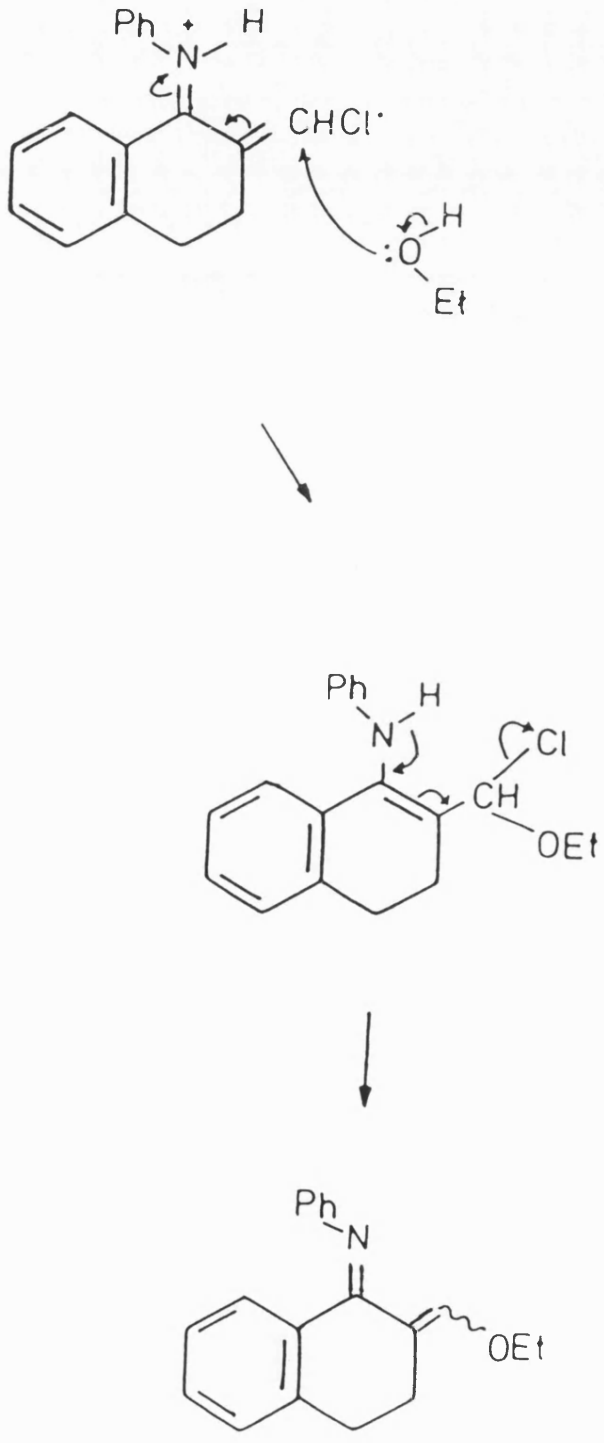
Enamines are known to react with dichlorocarbene, thus, for example, the indole (104) forms an adduct (105) which on hydrolysis yields 3-formyl indole (107) or in non-aqueous conditions ring expansion occurs to afford a β-chloroquinoline (106)[98,99]. See scheme 16.

Thus the formation of product (103) may be rationalised by assuming that the enamine form of the imine/enamine tautomerism (refer to page 73) is involved which then reacts with the dichlorocarbene to yield the Zwitterion (108). From this at least two routes can be envisaged which would lead to the vinylether (103) as illustrated in scheme 17 on pages 71 and 72 the concept that the imine may show reactivity in the enamine form, now makes it possible to speculate that the imine unit of the



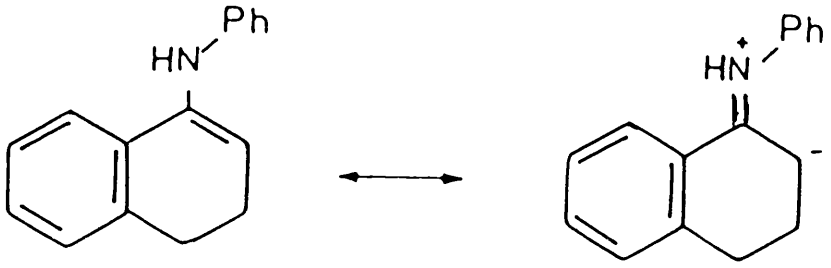
Scheme (16)


Ph
NH
H
:CCl2
Ph H
N+
Cl
C
Cl
H
(1083)
Ph H
N
Cl
Cl
H
Ph
N
H Cl
C
Cl
H
Ph H
N
CCl2
H+
Ph H
N
Cl
C
H
Cl

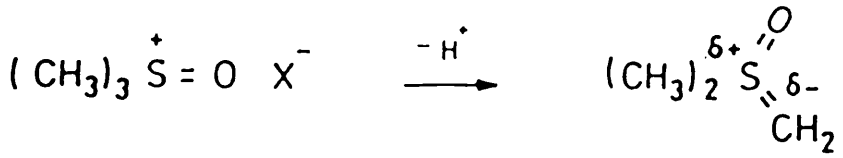


Scheme (17)

3,4-dihydro-1(2H)-N-phenylnaphthylimine (88) is not as reactive as the β-carbon atom of the enamine form of (88) towards dichlorocarbenes. Thus explaining the failure to form the expected dichloroaziridine compound.

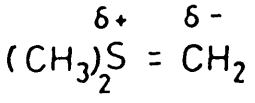


Corey and Chaykovsky[54,55,56,57] have studied behaviour and reactions of sulphonium ylides. They observed that trimethylsulfoxonium halides (109) underwent proton transfer to strong base with the formation of a reactive substance of considerable utility which could reasonably be formulated as dimethylsulphoxonium methylide (110).



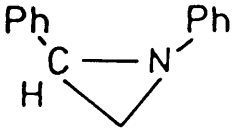
(109) (110)

Solutions of the ylide (110) in dimethyl sulphoxide were prepared from the iodide or chloride salt (109) by stirring with one molecular equivalent of powdered sodium hydride in an inert atmosphere. Another useful ylide (111) was similarly prepared by base treatment of trimethylsulphonium iodide.

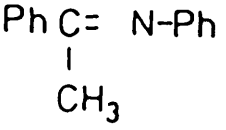


(111)

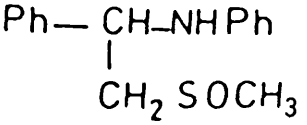
Both ylides are nucleophiles and both function to transfer methylene to certain electrophilic unsaturated linkages, including C=O, C=N, C=S and, in certain cases, C=C. The less reactive oxosulphonium ylide interacts with the carbonyl function of aromatic aldehydes and ketones to form oxiranes and with α,β-unsaturated ketones which are Michael receptors to form cyclopropyl ketones. The sulphonium ylides (111) reacts with the same substrate to give oxiranes exclusively, even with α,β-unsaturated carbonyl systems. Furthermore, Corey found that this ylide attacks the C=N bond of benzylideneaniline to give three products: 1,2-diphenylaziridine (112, 44%), acetophenone anil (113, 22%) and the amino sulphoxide (114, 19%).



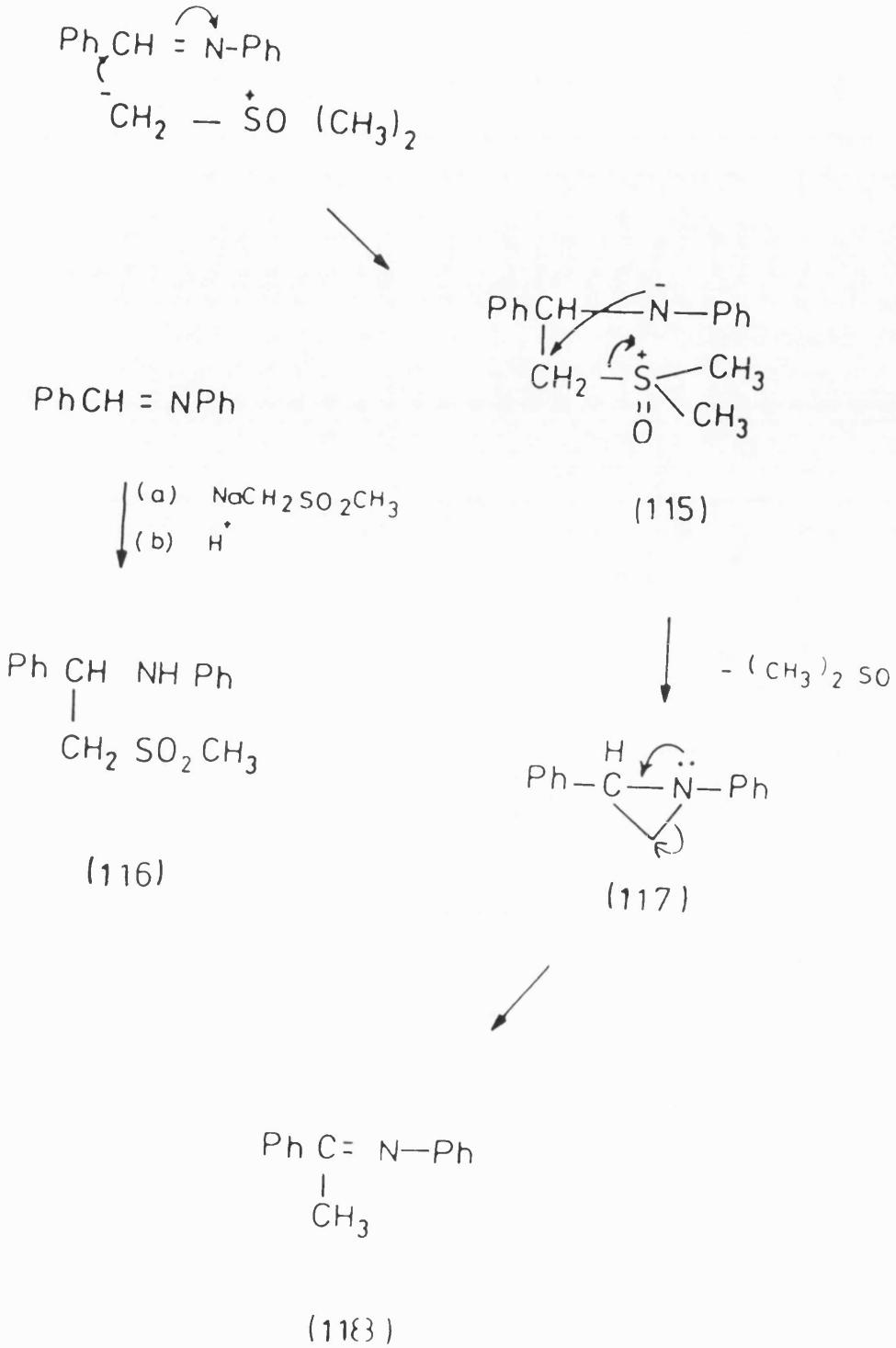
(112)



(113)



(114)

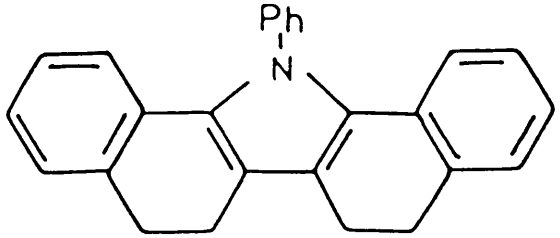

Ph CH = N-Ph
CH2 — SO (CH3)2
PhCH = NPh
(a) NaCH2SO2CH3
(b) H+
Ph CH NH Ph
CH2 SO2 CH3
(116)
PhCH—N—Ph
CH2 — S — CH3
O
CH3
(115)
- (CH3)2 SO
H
Ph—C—N—Ph
(117)
Ph C= N—Ph
CH3
(118)

Scheme (18)

These products[29,57] can be considered to arise firstly through the interaction of the negatively charged end of the ylide with the carbon atom of the imine to give the intermediate (115). This may eliminate dimethyl-sulphoxide to afford the aziridine (117) which may isomerise to the imine (118) by a 1,2-proton shift with concomitant ring-opening. Structure (116) is less easy to rationalise but its authenticity is proven by the fact that it is also made when methylsulphonyl anion ($\bar{C}H_2$-SO_2CH_3)is added to the parent anil. See Scheme 18.

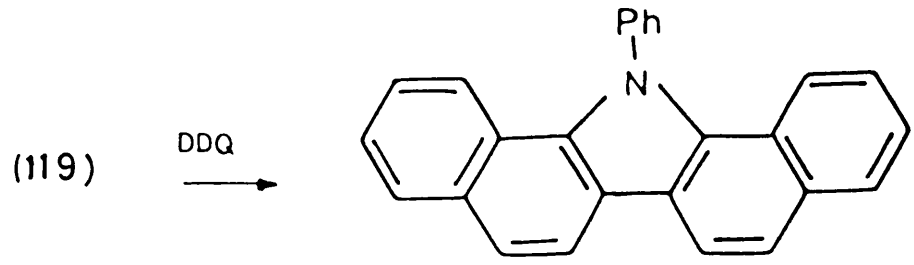
Applied to the imine (88) it was found that the ylide (111) did not give rise to any products analogues to those determined by Corey. Indeed using sodium hydride as the base to generate the ylide the imine was returned unchanged. However, when n-butyllithium was employed a product was obtained although its formation was very slow and, as later was discovered, depended on the presence of oxygen.

The molecular ion of this product was observed at m/z 347 corresponding to the formula $C_{26}H_{21}N$. Despite this rather high molecular weight compared to that of the starting imine m/z 221, or any expected product, the ^1H n.m.r. spectrum was quite simple and showed only one set of five proton resonances associated with a single phenyl group. On the other hand, there were eight other aromatic protons resonating as only four signals, i.e. each was due to two identical, or nearly, identical hydrogen atoms, similarly only one A_2M_2 system was observed, but this integrated to eight protons. Overall, this evidence pointed to 13-phenyl-[a,i]dibenzo-5,6,7,8-tetra-hydrocarbazole (119) as a likely structure for the first product and this was confirmed by a single crystal X-ray structure determination.



(119)

Oxidation of (119) was achieved using hot dry benzene as a solvent and the reagent 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). A more polar spot appeared on the analysis after a period of $^1/_2$hr reaction time. The crude product (0.045g) from the reaction was columned on silica using 50% ether in 60-80° petroleum ether to give the pure form (0.010g) of (120) as indicated by its mass spectrometry. The starting compound had a molecular ion corresponding to 347 mass unit and the final product had 4 mass units less than that, i.e. equal to 343. This was due to the loss of 4 protons to give the fully aromatic pentacyclic (120).



(120)

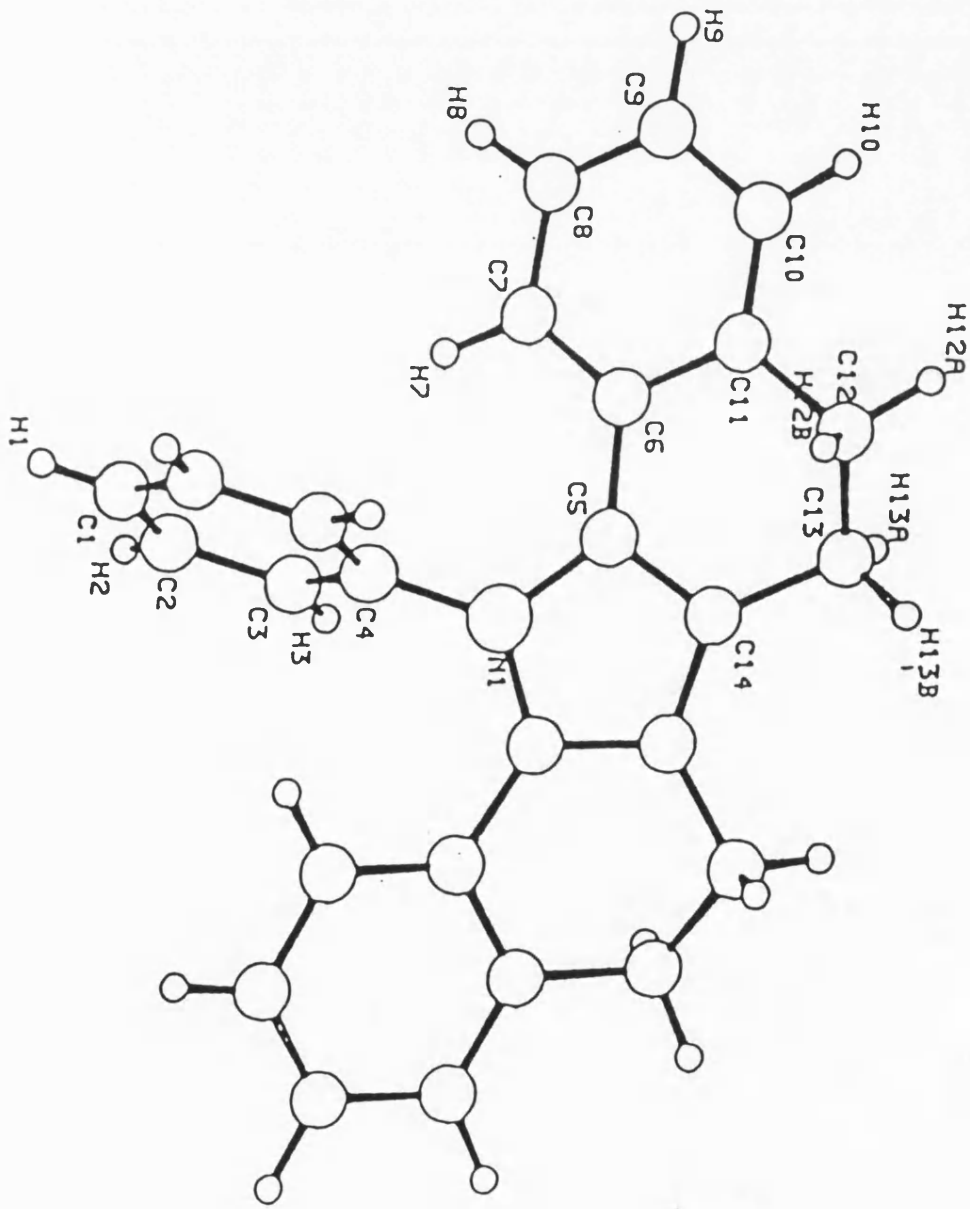

H9
C9
H8
H10
C8
C10
C7
H12A
C12
H7
C11
H12B
C6
H1
C5
C13
H13A
C1
H2
C2
C3
C4
H3
N1
C14
H13B

Fig. 3

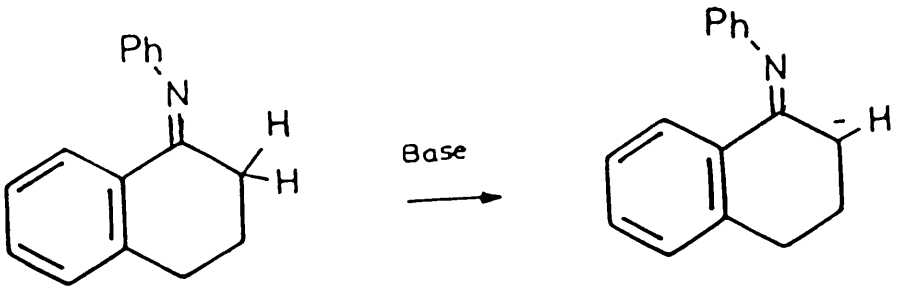
Fig. 4

C1-C2	1.365(3)	C1-C2-C3	120.9(2)
C2-C3	1.383(3)	C2-C3-C4	119.3(2)
C3-C4	1.384(3)	C3-C4-N1	120.1(1)
C4-N1	1.437(2)	C6-C5-N1	129.1(2)
N1-C5	1.388(2)	C14-C5-N1	107.9(2)
C5-C6	1.461(3)	C14-C5-C6	122.9(2)
C5-C14	1.379(3)	C5-C6-C7	126.1(2)
C6-C7	1.396(3)	C5-C6-C11	115.5(2)
C6-C11	1.416(3)	C11-C6-C7	118.3(2)
C7-C8	1.387(3)	C8-C7-C6	120.4(2)
C8-C9	1.373(4)	C9-C8-C7	121.0(2)
C9-C10	1.390(3)	C10-C9-C8	119.3(2)
C10-C11	1.380(3)	C11-C10-C9	120.8(2)
C11-C12	1.514(4)	C12-C11-C10	120.6(2)
C12-C13	1.513(3)	C10-C11-C6	120.0(2)
C13-C14	1.501(3)	C12-C11-C6	119.3(2)
		C11-C12-C13	113.5(2)
		C12-C13-C14	108.9(2)
		C13-C14-C5	120.5(2)
		C5-N1-C4	126.0(2)
		C2-C1-C2Z	119.6(2)
		C5-N1-C5Z	108.0(2)
		C3-C4-C3Z	119.6(2)
		C5-C14-C14Z	108.0(2)
		C13-C14-C14Z	131.5(2)

The results of an X-ray analysis, of bond angles and lengths are summarised in figures (3) and (4), which confirm the overall symmetry of the structure which is so much in evidence from the ^{1}H n.m.r. data.

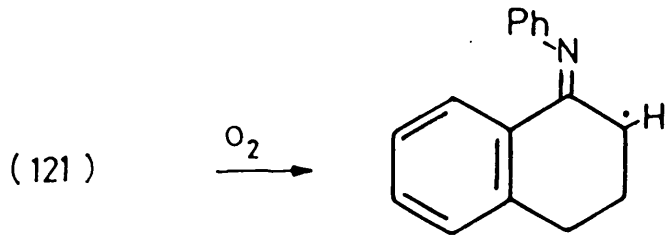
It was discovered that if oxygen was rigorously excluded from the reaction and also during the work up procedure, none of this polycyclic product was formed. Conversely, if air was deliberately admitted into the reaction vessel the yield of this product rose significantly. In view of this the following mechanism was proposed for its formation:

1. Deprotonation of the imine by n-butyllithium to afford the anion (121).

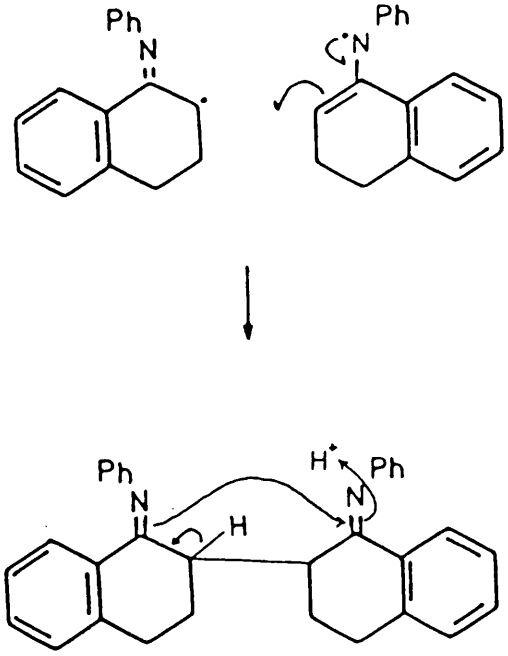


(121a) (121)

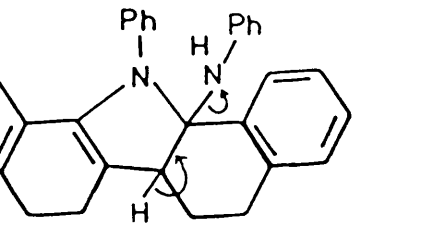
2. Oxidation of the anion by oxygen yielding the radical (122).



(122)



(123)

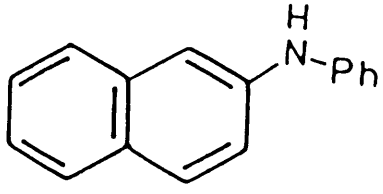


Scheme (19)

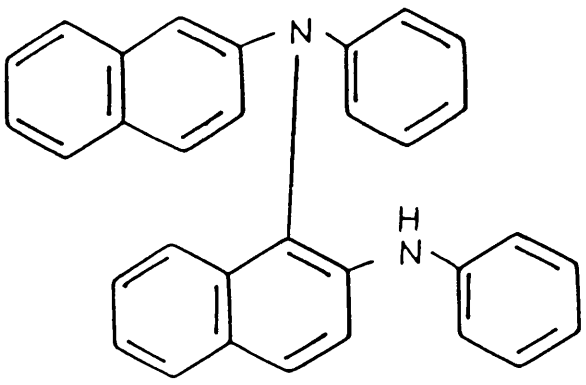
3. Dimerisation of the radicals to give the species (123) which eventually eliminated aniline, probably during acidic work up procedure, thereby creating a highly delocalised π-system in the product (119), as illustrated in scheme 19.

Support for this hypothesis is as follows: the product was still formed if dimethylsulphonium ylide was omitted. Other strong bases such as lithium diisopropylamide could be used and with this particular base followed by exposure of the reaction mixture to oxygen the yield of the pentacycle was increased to 40%.

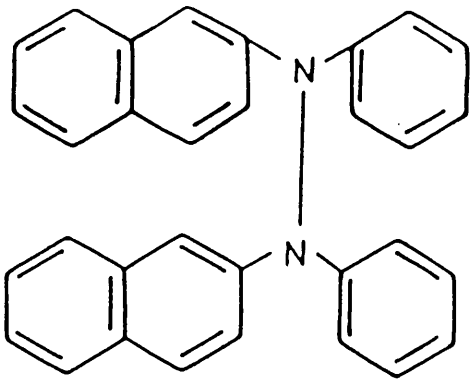
In a paper published by Angert and Kuzminskii[58] the infra-red absorption curves for N-phenyl-2-naphthylamine (124) after oxidation with molecular oxygen were analysed and it was assumed that products of the type (125 and 126) were present:



(124)

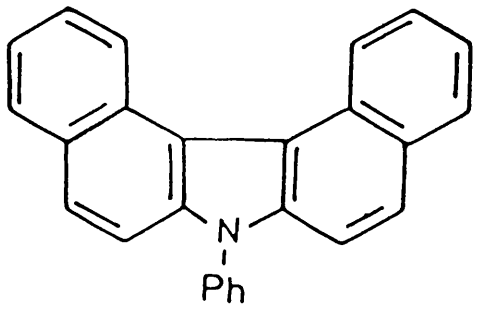


(125)



(126)

Angert and Kuzminskii were apparently unaware that experiments carried out at the Esso Research and Engineering Company long before their paper was published showed that permanganate oxidation of the amine (124) yielded a mixture of oxidation products containing product (125) and also 7-phenyl-dibenzo (c,g) carbazole (127).



(127)

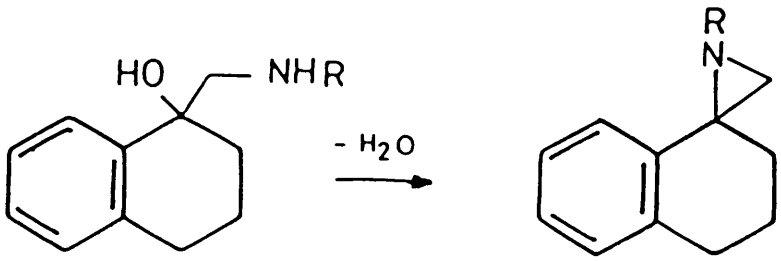
Both these compounds obviously arise through a radical coupling reaction and this provides some circumstantial evidence in favour of the postulated scheme for the oxidation and coupling of the enamine (121a).

CHAPTER TWO

THE USE OF α,β-AMINOALCOHOLS AS INTERMEDIATES FOR THE SYNTHESIS OF AZIRIDINES

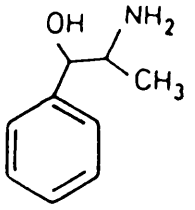
2.2.1 INTRODUCTION

Another approach to the desired aziridine structure (129) might be through the dehydration of α ,β - aminoalcohols of the type (128).

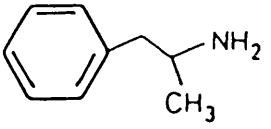


(128) (129)

It is therefore relevant to review briefly the literature concerning (a) the synthesis of α ,β - aminoalcohols and (b) their chemical behaviour. The volume of literature is considerable due to the useful pharmacological properties exhibited by a number of these aminoalcohols.



(130) Ephedrine



(131) Amphetamine

Many years ago Nagai[59,60] was able to show that the active principal of the Chinese drug Ma Huang (extracted from plants of Ephedra genus) is ephedrine (130). Since then numerous synthetic analogues of this structure have been made in an attempt to improve upon the sympathomimetic effects which ephedrine has on the central nervous system.

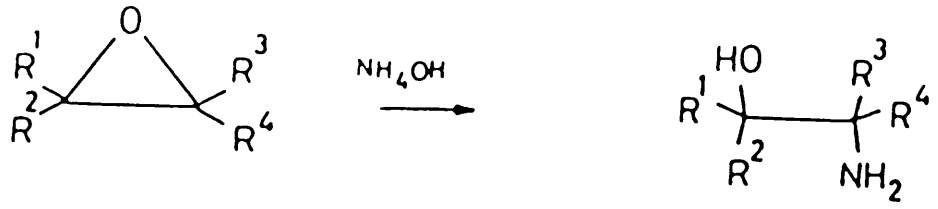
It is now understood that the ephedrine-like structures, as well as the closely related amphetamines (131), act to release certain neurotransmitting agents in vivo. [61,62]

2.2.1.1 Synthesis of aminoalcohols

2.2.1.1.1 From epoxides

One major route to α,β - aminoalcohols is via the ring-opening of epoxides with ammonia or amines.

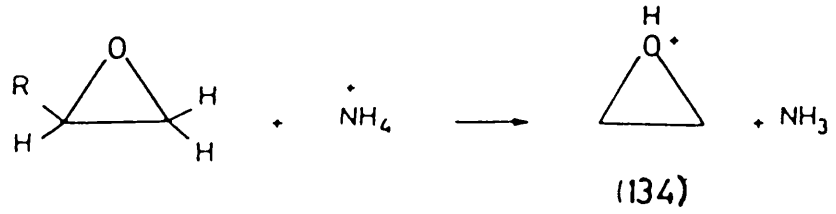
Early work by Schwenk[64] and Batalin[65] and by Lucas et al [63] on the reaction of 2,3- epoxy butane (132) with aqueous ammonia has already shown that this is a viable pathway to amino alcohols (133). No heat is required as simple agitation of the substrate and reagents over the course of several days serves to effect nucleophilic ring opening.



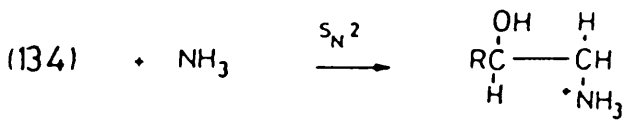
(132) (133)

Obviously the time factor and the large volume of aqueous ammonia normally employed are major disadvantages in these reactions. Consequently the use of pressure vessels is now recommended, in this way the reaction proceeds to completion within an hour or less .

Water is very necessary and it has been demonstrated[66,67] that no reaction occurs in anhydrous liquid ammonia. Less than one molar equivalent of water lowers the product yield and it is considered that ammonium ions act as catalysts (proton sources) in the ring-opening process:[118]



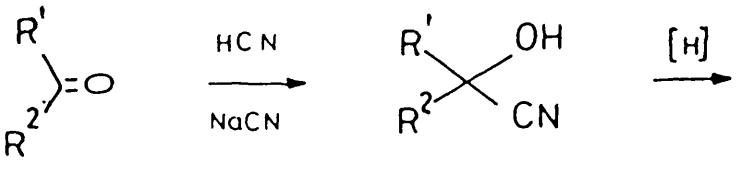
(134)

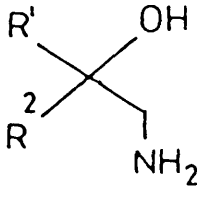


(135) trans addition

2.2.1.1.2 From cyanohydrins

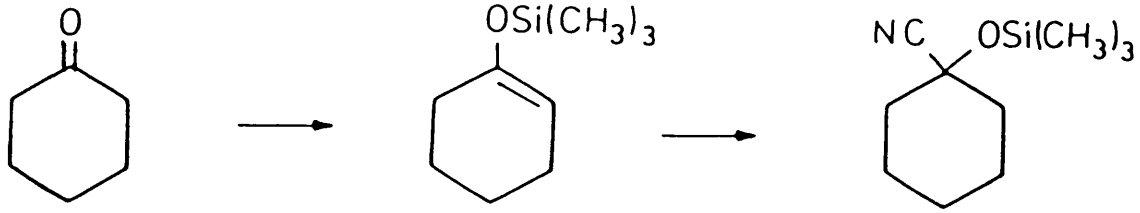
An obvious route to α ,β - aminoalcohols is the reduction of cyanohydrins and this is widely used:





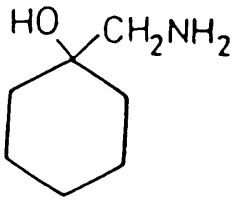
In the last decade or so a new synthesis of α ,β - aminoalcohols has been reported by Parham.[68] Cyclohexanone was converted into silyl ether (136) by conventional methods and this derivative was added to excess liquid hydrogen cyanide containing a catalytic amount of sulphuric acid. After some hours the α-cyanocyclohexyl trimethyl silyl ether (137) was formed, which was reduced and hydrolysed to the final product (138).

This method is especially valuable for ketones which may not easily form cyanohydrins or condense with nitromethane and to avoid the use of liquid hydrogen cyanide the following modification to the synthesis has been recommended. The reagent trimethylsilylcyanide is employed in reaction with the carbonyl compound leading directly to the corresponding α - cyanotrimethylsilyl ether. Aldehydes react rapidly whereas ketones are less reactive and even though the addition of zinc iodide promotes the reaction rate, it is clear that steric effects may still present a problem.



(136) (137)

1. $LiAlH_4$
2. H_2O



(138)

74 5 %

A "one-pot" synthesis of silylated cyanohydrins is reported by Duboudin,[69] which has the following advantages:

(a) Standardized conditions for many carbonyl compounds

(b) Short reaction times (a few hours)

(c) Room temperature is required

(d) No silyl enol ether formation or formation of higher molecular weight materials is noted.

This reaction is accomplished in two steps; the formation (without-isolation) of trialkylsilyl cyanide from chlorotrialkylsilane and cyanide ion, followed by the reaction with a carbonyl compound.

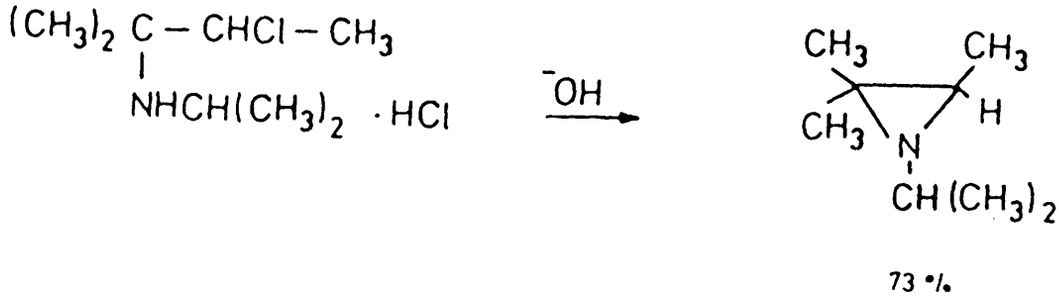
2.2.1.2 Cyclisation reaction of β- aminoalcohols

There are two useful aziridine synthesis which depend upon the cyclisation of β-aminoalcohols : the first is employed to form the aziridine directly from the aminoalcohol; and the second gives rise to the intermediate oxazolidinones which in turn may form the aziridine, as discussed later.

(a) Direct cyclisation

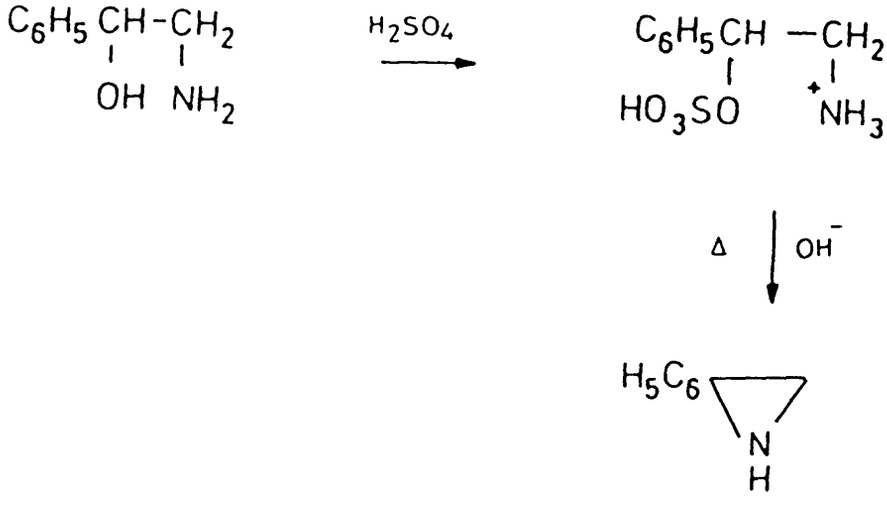
(i) In the Gabriel[71,73] method it is usual to convert the alcoholic function into a "good leaving" group, such as a halogen atom, prior to cyclisation.

(ii) In the Wenker method [72,73,74] the β- aminoalcohol is reacted with sulphuric acid to yield the β- amino hydrogen sulphate. This is then heated with alkali to give the aziridine with the loss of sulphuric acid.



73 %

Gabriel Method



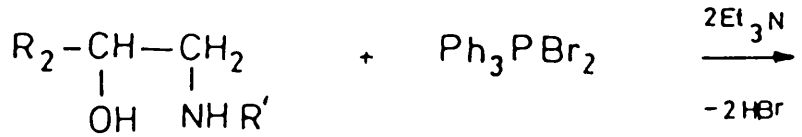
Wenker Method

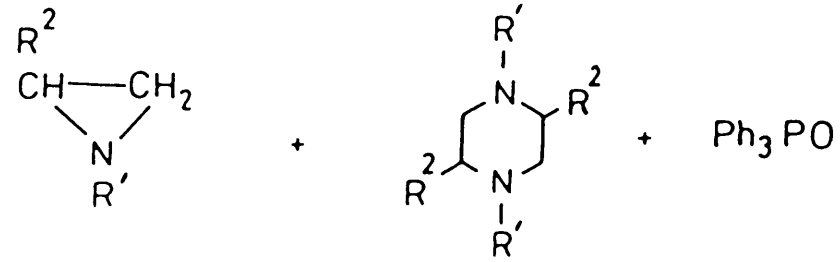
In the Gabriel synthesis, care must be taken to ensure that the product is not contaminated with volatile chloroamine which may initiate polymerisation. For this reason, the Wenker reaction offers some advantage

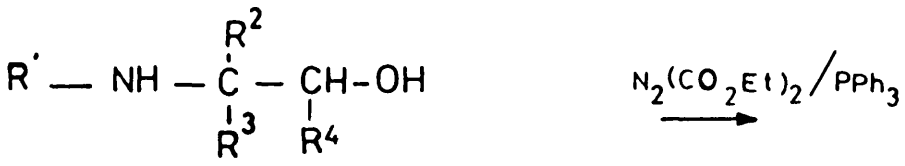
in ease of reagent handling, but side reactions [75] are known to interfere. For example, dehydration occurs when the hydroxyl group is attached to a tertiary carbon atom.

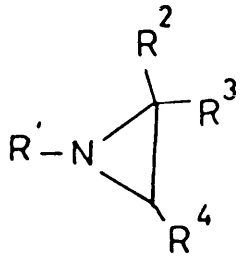
In 1970 a report [76] on the use of aminoalcohols in aziridine synthesis appeared which recommended triphenylphosphine dibromide as the cyclisation reagent under mild conditions. Prior to this report, Deyrup and Moyer [77] attempted the reaction of β-aminoalcohols with phosphorus pentachloride in the presence of triethylamine in order to form the aziridine ring, but this was unsuccessful.

Using the new reagent the reaction works well although 1,4 - piperazines are sometimes formed as by products and this can be a serious problem. This reaction is outlined below:









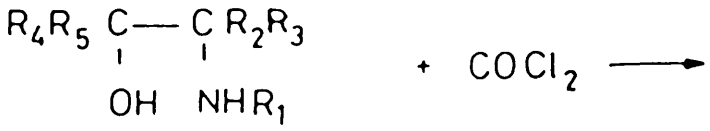
		Yield %
(139)	$R_1 = C_6H_5CH_2$; $R_2 = CH_3$; $R_3 = R_4 = H$	59
(140)	$R_1 = C_6H_5CH_2$; $R_2 = R_3 = H$; $R_4 = CH_3$	90
(141)	$R_1 = C_6H_5CH_2$; $R_2 = R_3 = CH_3$, $R_4 = H$	89

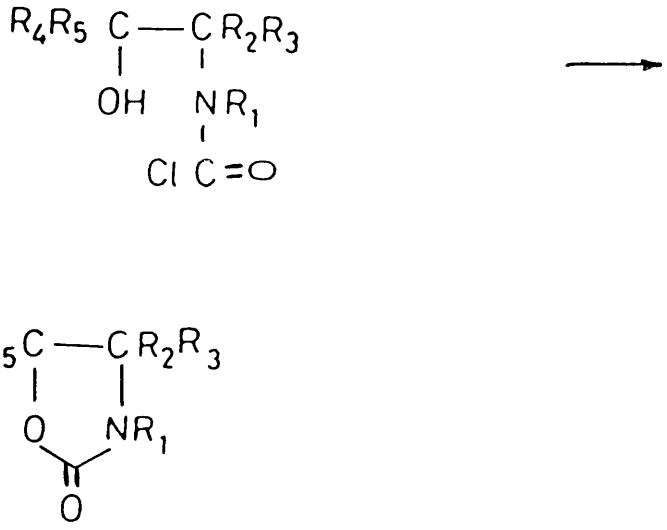
Scheme (20)

A recent report by Pfister [78] described a one-pot synthesis of aziridines from 2- aminoethanols. This synthesis involved the use of the Mitsunobu reagent, triphenylphosphine/diethylazodicarboxylate. Even though this reaction is a traditional one, further investigation was provided by Pfister's report. He found that the reagent involved was not of a general nature as it did not react with some aminoalcohols. However, no account for these failures was given. Most of the other aminoalcohols which took place in the reaction were found to contain at least one substituent attached to either carbon atom between oxygen and nitrogen atoms. Good yields of aziridines were observed during these reactions; see scheme 20.

(b) Cyclisation of β- aminoalcohols to oxazolidinones

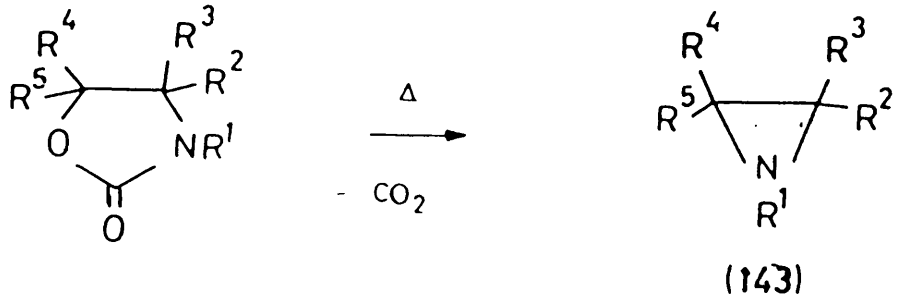
β- Aminoalcohols are frequently used [79] in the synthesis of oxazolidinone. At least one replaceable hydrogen in the amino group was found to be an essential requirement in this synthesis. The reaction outlined below shows the formation of 1,3 - oxazolin - 2 - one (142) using phosgene.





(142)

In the thermolysis of (142) carbon dioxide is usually expelled and the aziridine (143) is formed.



(143)

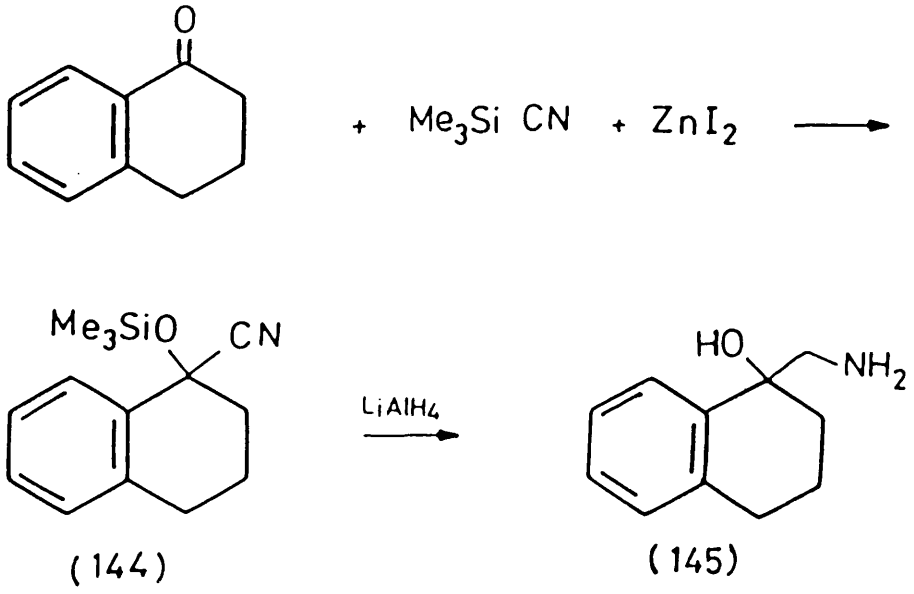
CHAPTER TWO

2.2.2 DISCUSSION

2.2.2.1 Attempted cyclisation of α,β- aminoalcohol derivatives of α - tetralone

Following the unsuccessful attempts to form the aziridine type compound described in the previous chapter, a different approach is described in this section. This time, the cyclisation of aminoalcohols derived from α-tetralone is investigated.

The aminoalcohol (145) shown below was prepared by Evans [80] in 1974 from trimethylsilylcyanide and α- tetralone in a reaction promoted by zinc iodide. Thus the intermediate siloxycyanide (144) was obtained and reduced by lithium aluminium hydride to afford the desired compound (145) in 95% yield.

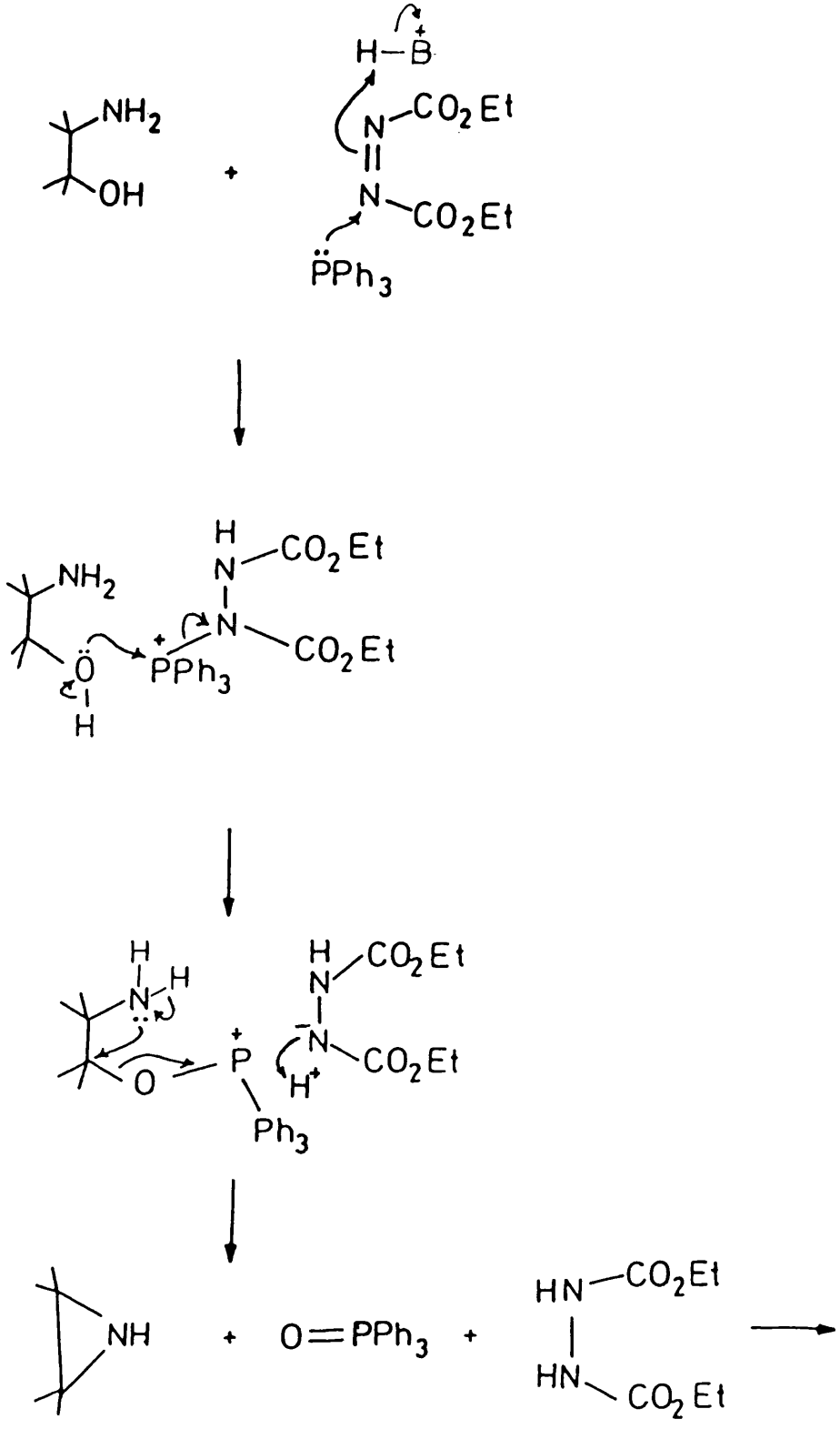


(144) (145)

A publication by Beeley [31] also stated the use of Evans method to form a similar derivative of tetralone which was employed to obtain the novel cardiovascular agent N - [(6- methoxy - 1,2,3,4 - tetrahydro-naphthalene - 1 - yl) methyl propanamide, see page 39 .
In view of this endorsement, Evan's route was employed during this research programme and a good supply of the starting amino alcohol (145) was obtained for the work concerned.

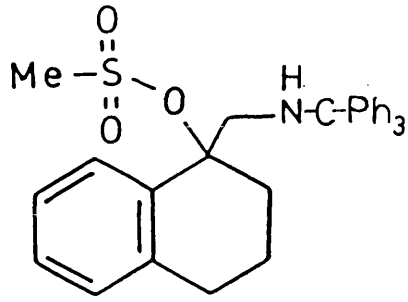
Rather than using an acidic reagent to cyclise the amino alcohol (145) during this research procedure, the so called DEAD/CAT reaction was attempted. The DEAD/CAT is the short form for the reagent diethylazodicarboxylate and the catalyst triphenylphosphine which have been used by other authors, as described on page 93 . The mechanism involved the activation of the hydroxyl group by the diethylazodicarboxylate and the triphenylphosphine, thus providing a "good leaving" group to be displaced intramolecularly by the lone pair of electrons on the nitrogen atom of the amino function. This illustrated in scheme 21.

This cyclisation failed when applied to the amino alcohol (145) or the N-alkyl and N-aryl derivatives of this material.
Other means of hydroxyl group "activation" such as the formation of p-toluenesulphonyl or O-mesyl derivatives were subsequently attempted. The p-toluenesulphonyl derivative was difficult to form and the mesyl compound (146) proved to be unstable in contact with air. The instability of (146) was encouraging in terms of its reactivity, but treatment of sodium hydride in tetrahydrofuran did not cause any reaction and the starting material was

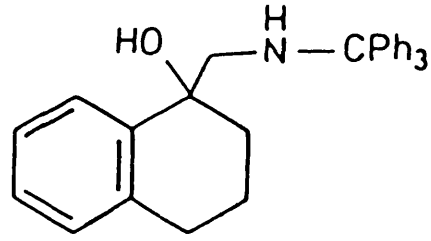


Scheme (21)

returned unchanged. Similar failures occurred when sodium hydride was replaced by triethylamine and when the N-trityl derivative (147) was used as the starting aminoalcohol.

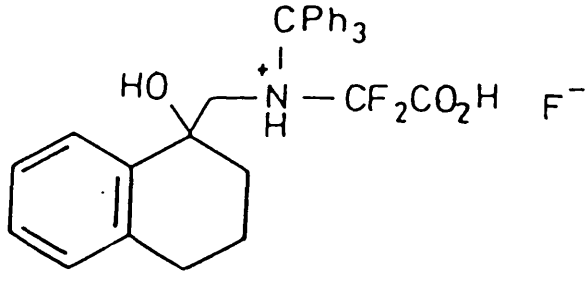


(146)



(147)

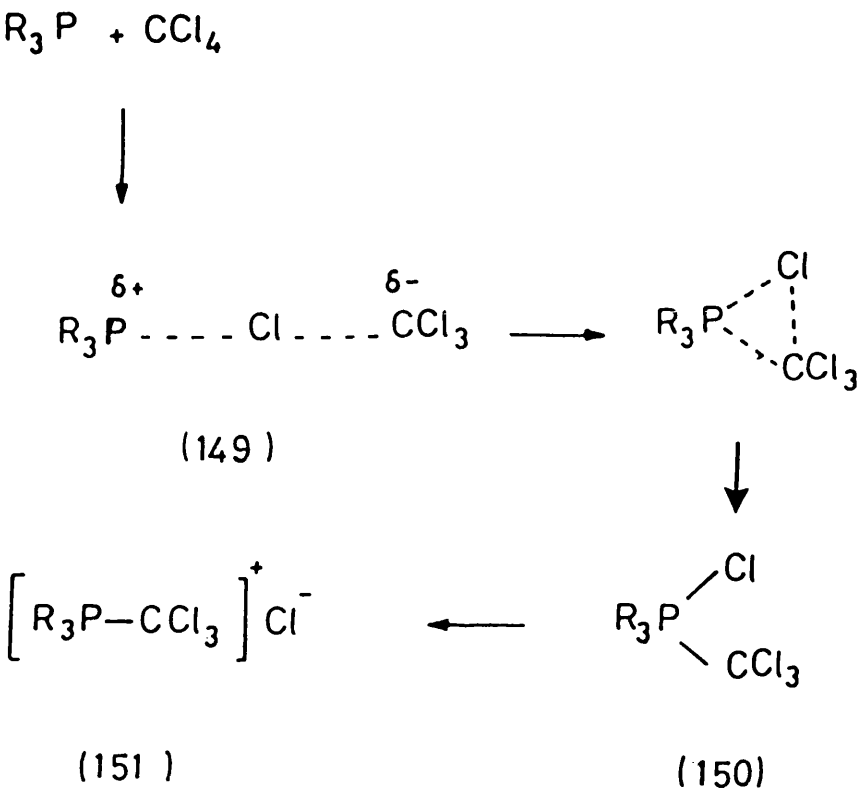
N-Butyllithium caused total destruction of (146), whereas treatment of 147 with trifluoro-acetic acid may simply form the corresponding ammonium salt (148) which reverted back to the starting aminoalcohol after treatment with a base.



(148)

Cadogan [81] has described the conversion of aminoalcohols into aziridines by the use of triphenylphosphine (PPh_3) and carbon tetrachloride (CCl_4). The mechanism consists of an ionic route and is initiated by the polarizing action of the dipolar phosphine on the symmetrical but readily polarizable tetrahalogeno methane. This possibility is outlined in scheme 22.

Scheme(22)

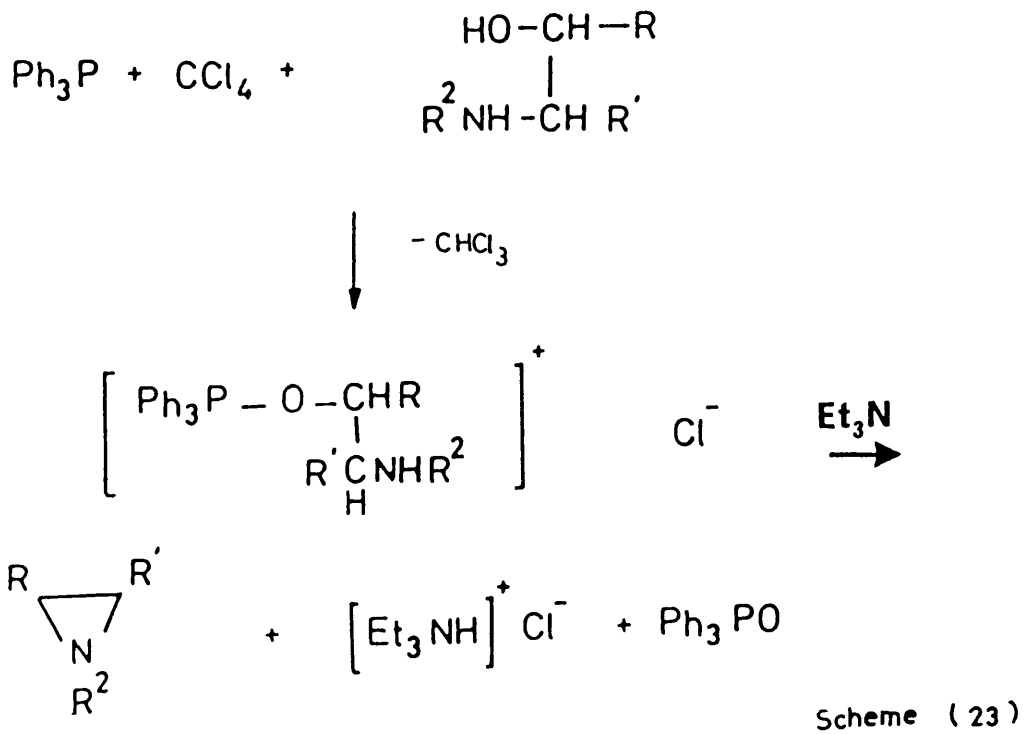


(149)

(151)

(150)

In the Ph_3P- CCl_4 system however, the trichloromethyl phosphonuim chloride (149) can only be regarded as a short lived and a highly reactive intermediate.

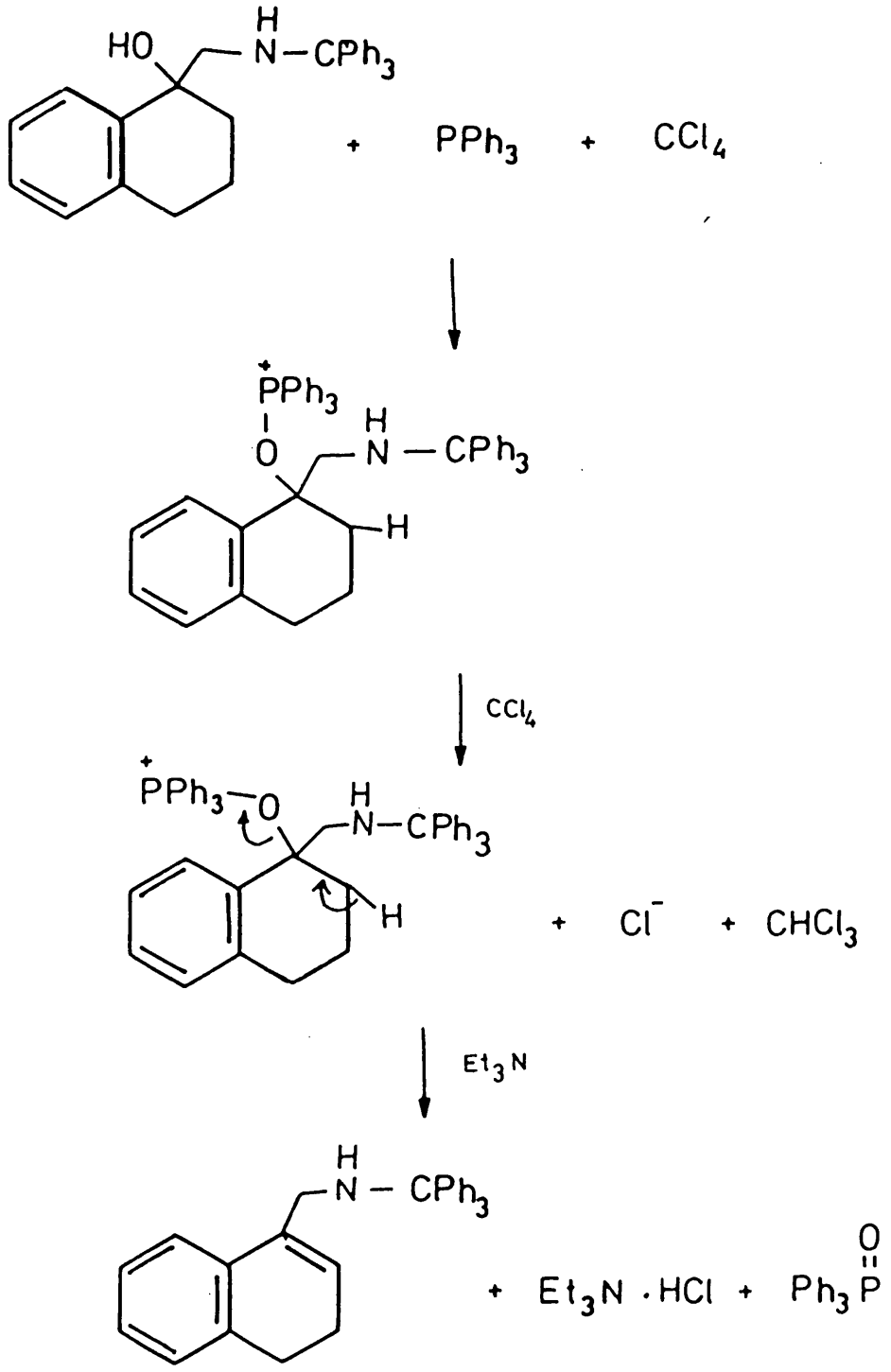


Scheme (23)

The reaction is fastest in acetonitrile and slowest in pure excess carbon tetrachloride. Comparative kinetic studies indicate that charge separation is the rate determining step which depends markedly on the solvation properties of the solvent.

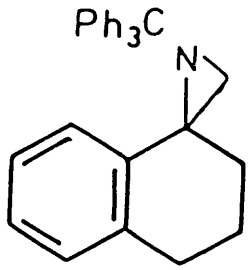
The action of PPh_3-CCl_4 on N- substituted aminoalcohols has been used by Cadogan to obtain a single step synthesis to the aziridines under mild conditions, as shown in scheme 23. The ring closure from the alkoxy phosphonium salt occurs with inversion as in similar synthesis by means of triphenylphosphine dibromide. Aminoalcohols not substituted on the nitrogen atom undergo phosphorous - nitrogen linkage as the predominant reaction so that this procedure is unsuitable for the preparation of aziridines.

As Cadogan succeeded in forming aziridines via the phosphine route, and only when N-substituted aminoalcohols were the starting materials, it was decided to use the readily available N-tritylaminoalcohol (147) for the same purpose. Instead of obtaining the aziridine (152) the compound (153) was produced in 40% yield. The spectral data of this compound is as follows: The ^1H n.m.r. spectrum (100MHz) showed signals due to 19 aromatic protons (δ7.00 - 7.6 ppm), a vinylic proton (δ6.24 ppm,t,J = 5Hz) and the resonance of two N-methylene protons as a singlet (δ3.08 ppm). The i.r. spectrum gave a double bond absorption band at 1600 cm^{-1} together with the aromatic absorptions at 1490 and 1450 cm^{-1}.

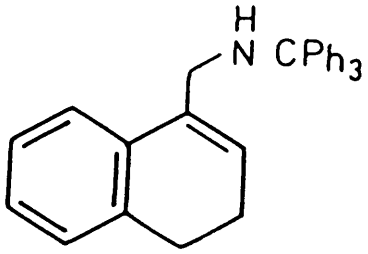

HO
H
N—CPh3
+ PPh3 + CCl4
PPh3
O
H
N—CPh3
H
CCl4
PPh3
O
H
N—CPh3
H
+ Cl⁻ + CHCl3
Et3N
H
N—CPh3
+ Et3N·HCl + Ph3P
O

Scheme (24)

A high resolution mass measurement indicated the molecular formula $C_{30}H_{27}N$. The structure is therefore shown below as the compound (153).



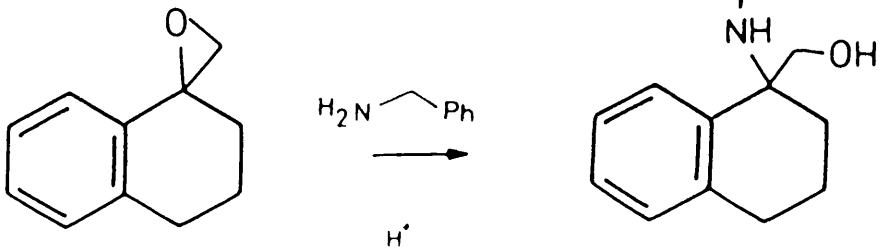
(152)



(153)

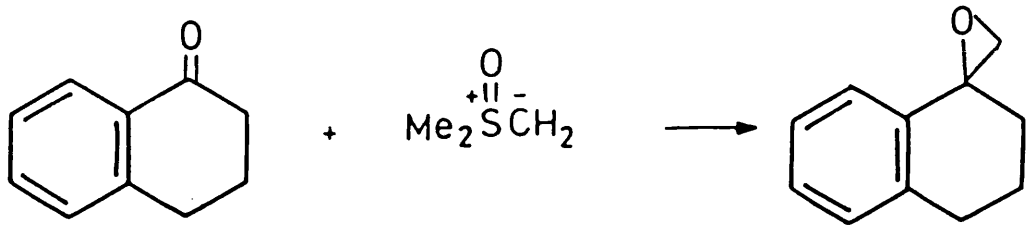
There are two possible reaction pathways to this compound. The first is shown in scheme 24 and the second follows from the Cadogan's mechanism (see p. 98). Unfortunately no ring closure was achieved, possibly because the amino function is insufficiently nucleophilic.

In another attempt to form the aziridine the epoxide (154) was made. It was expected that this compound when treated with benzylamine would open regioselectively to give the aminoalcohol (155).

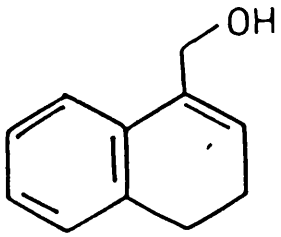


(154) (155)

This epoxide was synthesised by reacting α-tetralone with either dimethyl-sulphonium or dimethyloxosulphonium methylides in a mixture of dry dimethyl-sulphoxide and tetrahydrofuran. The epoxide was obtained in 98% yield and the spectroscopic data of this compound corresponded to the literature values.[82]



When benzylamine was reacted with the epoxide (154) an amino alcohol was not obtained, instead the dihydronaphthylalcohol (156) was formed.

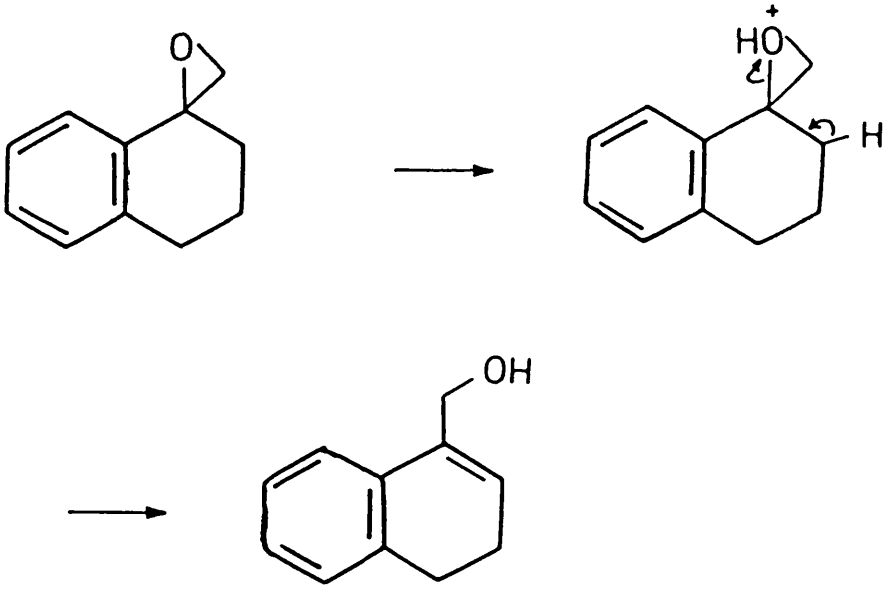


(156)

The i.r. spectrum of this product exhibited a hydroxyl band at 3400 cm^{-1}, and the ^1H n.m.r. spectrum consisted of four proton resonances in the aromatic region, a triplet at δ 6.00pm (J = 4HZ) [due to resonance of the olefinic proton] and a singlet at δ 4.5 ppm, which arose from the signal of the methylene protons adjacent to the hydroxyl group. The remaining protons at C-3 and C-4 gave rise to a complex spin system at δ 2.2-3.0 ppm and the proton of the hydroxl group resonated as a broad singlet at δ 1.9 ppm.
In the mass spectrum the molecular ion peak occurred at m/z 160 which corresponded to the molecular formula $C_{11}H_{12}O$.

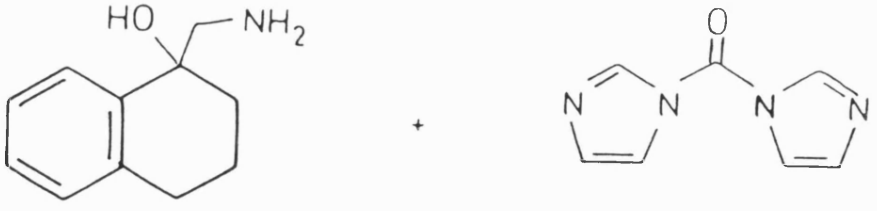
This alcohol (156) was produced on three occasions : in the first, hydrogen chloride was bubbled through a mixture of the epoxide (154) and benzylamine in dry dimethylformamide (DMF). This gave a 30% yield of the alcohol. Secondly, a similar yield of the same alcohol was obtained when p-toluenesulphonic acid was used instead of hydrogen chloride. However, the best yield (50%) of the alcohol (156) was obtained when the Lewis acid zinc iodide was used in dry tetrahydofuran.

The general mechanism, proposed to account for the formation of the alcohol is as follows: the epoxide oxygen atom was protonated and followed by subsequent elimination of the proton at C-2 of the tetrahydronaphthalene together with the ring opening of the epoxide.

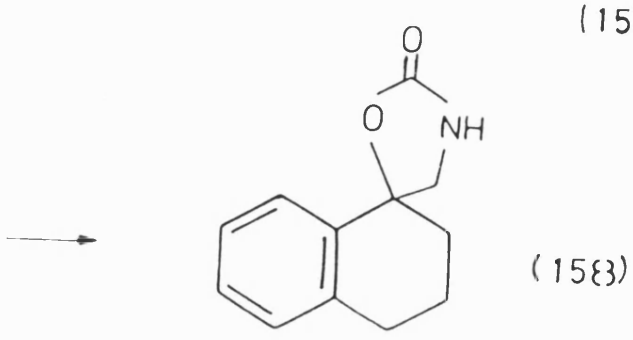


The final attempt to synthesise the aziridine via the aminoalcohol was to use oxazolidinones prepared from these aminoalcohols. It is known that oxazolidinones thermally extrude carbon dioxide forming aziridines as mentioned before:

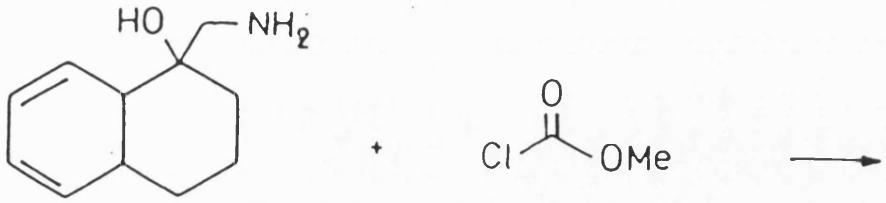
Thus, the 1,3-oxazolidin - 2 - one (158) was prepared using a classical method. Phosgene was reacted with the aminoalcohol (145) in the presence of a base. The type of base used had a significant effect on the final yield of the oxazolidinone. In the case of pyridine, high initial yield of a product indicated by the analysis (i.e. one major spot) of the reaction mixture; but after aqueous work-up a low yield resulted. Dry potassium carbonate was also employed but a slower reaction rate was noted. The best and most convenient reagent is the N,N'-carbonyl-dimidazole (157). In this case the work-up of the reaction mixture involved extraction with carbon tetrachloride (CCl_4) to remove excess imidazole.

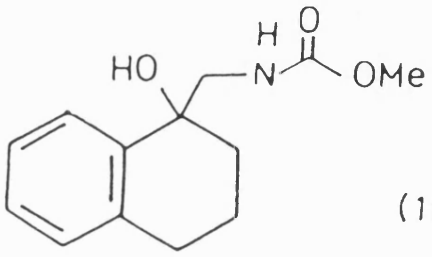


(157)



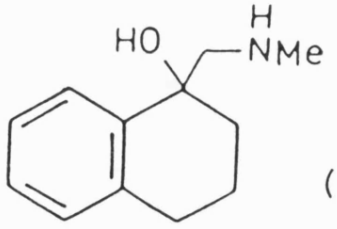
(158)





(159)

(159) + $LiAlH_4$ ⟶



(160)

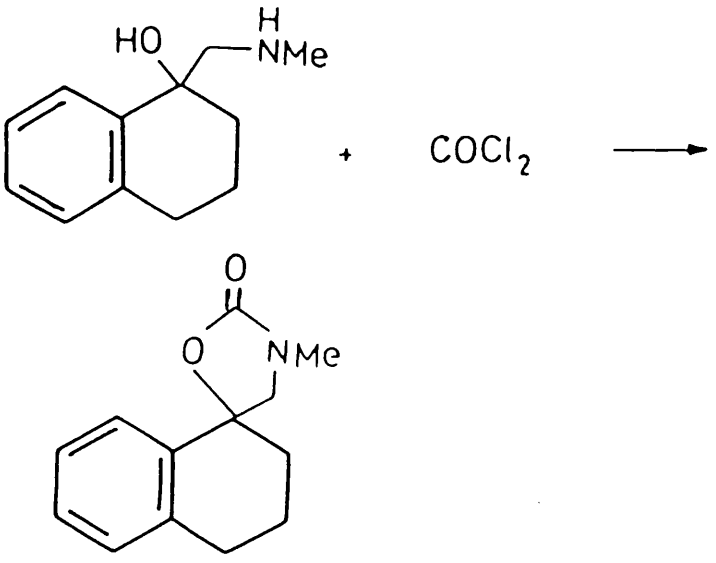
Scheme (25)

The i.r. spectrum of (158) exhibited an -NH absorption at 3300 cm^{-1} and a carbonyl band at 1750 cm^{-1}. The ^1H n.m.r. (100 MHz) consisted of four resonances due to aromatic protons (δ 6.65 ppm), a quartet for signals of the N-methylene protons (δ 3.64 ppm $\underline{J}$ = 8Hz) and the signals of six aliphatic protons (δ 1.8 - 2.9 ppm).

High resolution mass spectrometric measurement gave a molecular ion peak at m/z 203 which agreed with the formula $C_{12}H_{13}NO_2$.

The N-methyl oxazolidinone (161) was also synthesised. This was achieved by initially reacting the aminoalcohol (145) with methyl chloroformate to give 1-(N-methylcarbamate aminomethyl) - 1,2,3,4 - tetrahydronaphthalene - 1 - ol (159) followed by reduction with lithium aluminium hydride ($LiAlH_4$) to yield the aminoalcohol (160), see scheme 25.

The N-methylaminoalcohol (160) was then reacted with phosgene in the presence of a base (see p.106) to give the N-methyloxazolidinone (161) in 50% yield.



(161)

Direct methylation of the oxazolidinone (158) to (161) was not successful. The spectral data of (161) is as follows: the i.r. spectrum showed a weak amino group absorption band at 3450 cm^{-1} and a strong one at 1750 cm^{-1}(C=O absorption). The ^1H n.m.r. (100 MHz) exhibited four aromatic proton resonances (δ 7.0 - 7.5 ppm), a quartet at δ 3.6 ppm, $\underline{J}$ = 6Hz corresponded to the signals of the N-methylene group and a singlet (δ 2.9 ppm) due to the resonance of the N-methyl group.

The high resolution mass measurement corresponded to the formula $C_{13}H_{15}NO_2$.

Thermolysis of (161) was investigated on a small scale. Its melting point was noted to be 84-86°C. Gradually the temperature was raised to 172°C and the colour of this compound darkened but no gas was evolved. This was then allowed to reach 240°C but still no gas evolution was observed. The analysis of the contents of the melting tube corresponded to that of the starting material. So clearly no decomposition had occurred. An attempted thermolysis using refluxing toluene also produced no reaction. Photochemical studies were not conclusive due to the complexity of the mixture as shown on the tlc. The solvent employed was dry benzene.

CHAPTER THREE

SYNTHESIS OF THE AZIRIDINES

2.3.1 INTRODUCTION

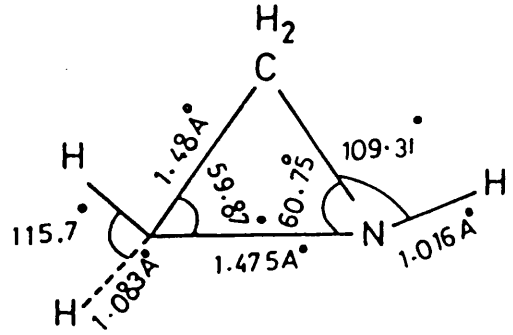
2.3.1.1 General aspects of the aziridines

Aziridines have attracted considerable attention in recent years because of fundamental academic interest in such compounds [83,84], as examples of highly strained reactive rings. Aziridines and some of their simple derivatives are produced commercially and they have found considerable use in many branches of applied chemistry, such as the manufacture of textiles, plastics, coating material and pharmaceuticals.

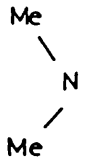
Dihydro-azirine, better known as aziridine or ethylenimine, and occasionally as azacyclopropane, was first prepared by Gabriel in 1888, although its cyclic structure was first recognised by Markwald in 1900. Data shown in scheme 26 was obtained from microwave spectrum of the vapour state of dihydro-azirine. The molecule is slightly twisted because the H-CH plane is at an angle of 87° to the ring plane.

The dipole moment of aziridine is 1.89 D and the strain energy of the ring is due to the distortion of most of the bond angles and distances from normal. The strain in the ring is also reflected in the change of the C-H bending frequency in the i.r. from its normal position 1465 cm^{-1} to 1475 cm^{-1} and the N-H vibration frequency 1441 cm^{-1} is lower than usually encountered in secondary amines 1460 cm^{-1}.

Scheme (26)

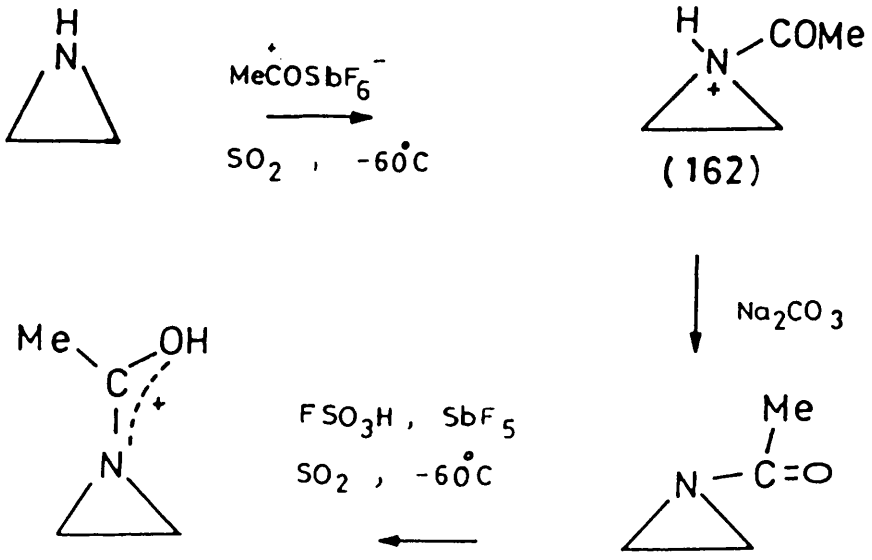


Aliphatic	C—C	1·54 A°
"	C—N	1·47 A°



111 ± 3°

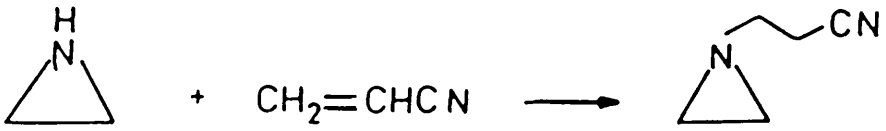
Scheme (27)



2.3.1.2 Stability of aziridines

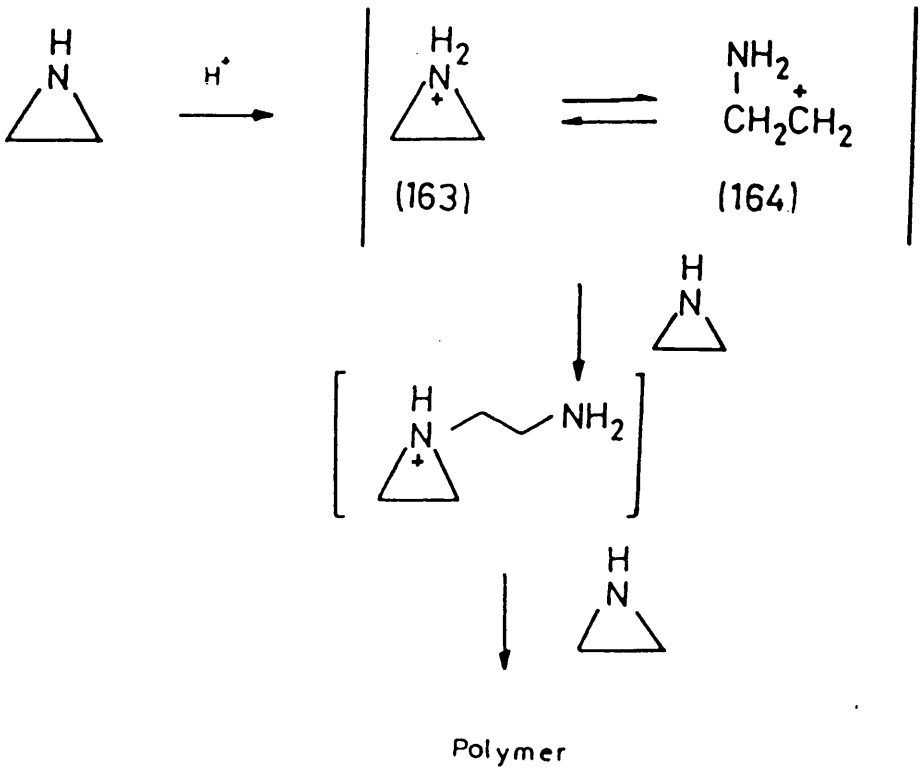
Ethyleneimine is not a very stable compound, as normally obtained. It is best stored over sodium hydroxide in sealed bottles in a refrigerator. It can behave as a secondary amine, although the ring strain often makes other reactions of more consequence, for example reaction with phenyl isocyanate and isothiocyanate gives the corresponding ureas. It complexes with metals, acid anhydrides or chlorides in the presence of alkali to give the N-acyl derivatives. It is interesting that acetylation of aziridine under forcing conditions gives the N-protonated salt (162), which is stable at 0°C, but protonation of 1- acetylaziridine normally occurs on the oxygen atom as illustrated in scheme 27.

As a secondary amine aziridine gives 1-chloro and 1-bromo derivatives with aqueous hypohalite and adds to activated double bonds:



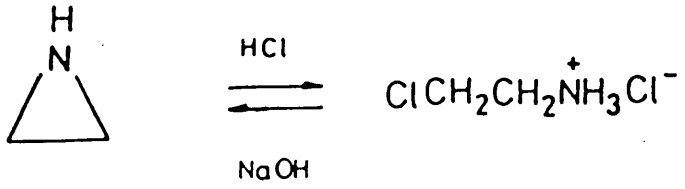
Although pure dry aziridine is comparatively stable, it polymerises in the presence of traces of water and rapidly (occasionally explosively) in the presence of acids. Carbon dioxide is acidic enough to promote this process which is not free radical in nature, as free-radical polymerisation inhibitors do not affect the reaction.

Aziridine is stable to bases, and it is thought that the polymerisation proceeds through iminium intermediates as indicated below:

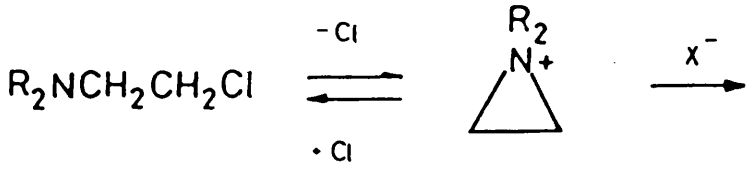


Kinetic studies and other evidence show that nucleophilic attack (by an uncharged aziridine) usually takes place on the cation (163) with simultaneous ring opening rather than on the corresponding carbonium ion (164).

Under proper conditions aqueous hydrochloric acid opens the aziridine ring to give 2-chloroethylamine in a way similar to its reactions with oxirane and thiirane. This ring opening is approximately second order, but re-cyclisation with sodium hydroxide is first order and quantitative. The rate constants for both types of reactions are greatly influenced by substitution.



N,N- Dialkylamino alkylhalides cyclise reversibly in dilute aqueous solution to yield aziridinium salts (165) which can be made to react with a variety of anions to give the corresponding products. The reaction with thiosulphate ion is very fast and is used to quantitatively estimate aziridines.



(165)

$R_2NCH_2CH_2X$

X^- OH^-, Cl^-, $EtCO_2^-$, $PhCO_2^-$, HCO_3^- and $S_2O_3^{2-}$

2.3.1.3 Reactions of aziridines

There are two principal properties that account for all reactions of aziridines which involve the aziridine ring[86]. The first is due to the reactivity of the aziridine nitrogen and the second is caused by the strained three-membered ring. The reactivity of the nitrogen atom may be attributed to the unshared pair of electrons and thus closely resembles the behaviour of other non-aromatic amines. Reactions due to the strained ring involve ring destruction or ring opening, forming either acyclic or ring expanded compounds.

Nitrogen substituted aziridines [87] may be broadly divided into two groups of compounds. These are: group A (activated aziridines), compounds in which the substituent is capable of conjugating with the lone pair of electrons on the aziridine nitrogen (eg the carbonyl group,making the aziridine nitrogen a tertiary amide nitrogen). Group B (basic aziridines) compounds in which there is no such substituent. Due to such conjugation in activated aziridines, reactions involving only the aziridine nitrogen are exhibited chiefly by compounds of group B. Thus, these reactions are similar to those of typical secondary and tertiary amines. Such reactions are known as ring-preserving reactions.

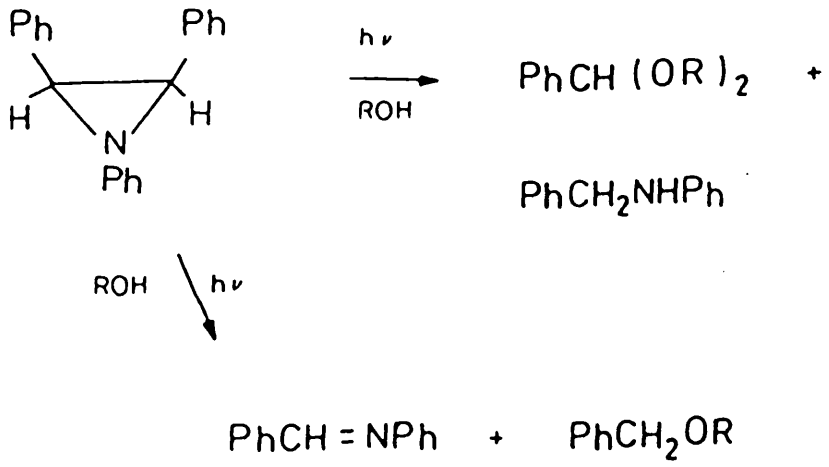
2.3.1.4 Photochemistry of aziridines

Investigation of the photochemistry of the three membered nitrogen heterocyclic ring[88] have demonstrated that these species are exceptionally reactive under the influence of ultra-violet light.

Irradiation may lead to geometrical isomerisation, rearrangement, internal hydrogen abstraction or photofragmentation, or photochemical valence tautomerisation.

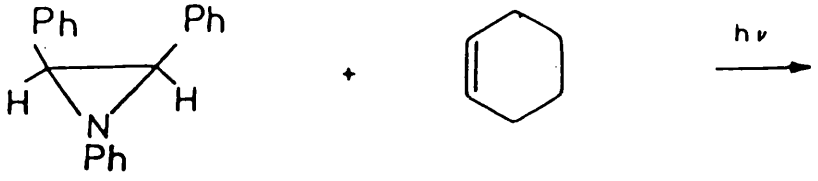
It has usually been found that the photolysis can best be described by a cleavage of the C-C bond of the aziridine ring followed by a multitude of possible secondary steps.

Irradiations of 1,2,3 - triphenylaziridine in various alcohols has been reported to give benzaldehyde acetals and N- benzalaniline. Competitive fragmentation gives N- (benzylidene) aniline and phenyl carbene, which is also trapped as the alkyl -benzyl ether as shown below:

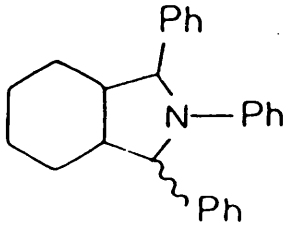


(166)

Additive reactions occur in the presence of alkenes thus a pair of steroisomeric 1,3- cycloaddition products having the 1,2,3-triphenyloctahydroisoindole skeletal structure (168) are formed upon photolysis of (167) in cyclohexene.

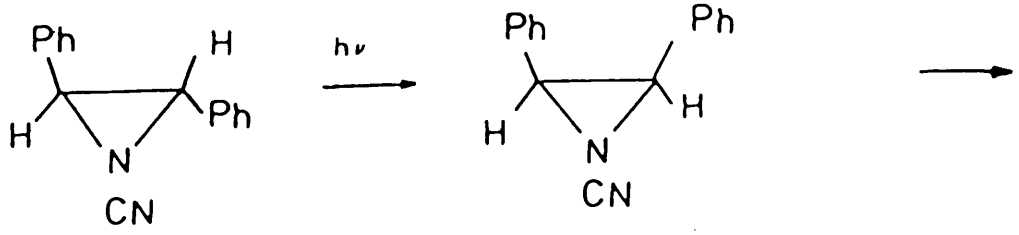


(167)

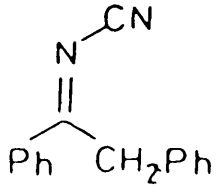


(168)

The photochemical behaviour of a number of related N- substituted diphenyl-aziridine has been studied . In the case of N-cyanodiphenylaziridine, irradiation at λ = 254 nm leads not to fragmentation but rather to clean isomerisation. While both stereoisomers rearrange to (171) on irradiation, only the <u>trans</u> - isomer undergoes stereoisomerisation to the <u>cis</u>-isomer.



(169) (170)

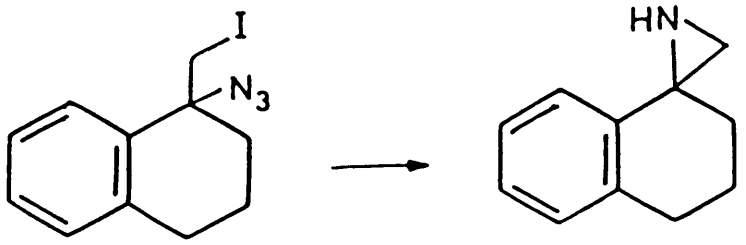


(171)

2.3.2 DISCUSSION

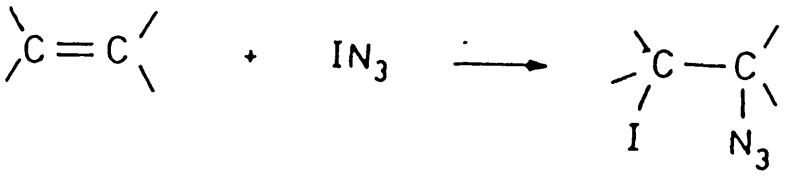
2.3.2.1 Synthesis of spiro [2',1] - 1 ,2 ,3 ,4 - tetrahydronaphthylaziridine

In this section, the synthesis of the aziridine (173) will be discussed. As mentioned previously, the use of various methods to obtain this compound proved unsuccessful, but when a modified Hassner's route[90] was employed a good yield of the aziridine (173) was obtained. The difference between the two cases is in the type of starting material used. In the first, the imine 3,4 - dihdro - 1 (2H) - N-Phenylnaphthylimine was used and in the second, 3,4 - dihydro (2H) - 1 - methylene naphthalene (182).

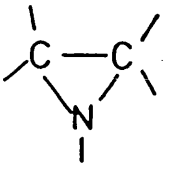


(172) (173)

This method[89,90,91,92] involved the use of the reagent iodine azide (IN_3) to prepare the iodoazide derivative (174). This was cyclised to give the aziridine (175).

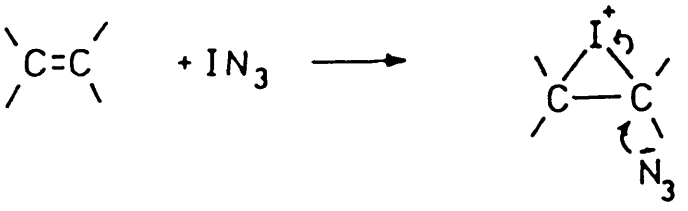


(174)



(175)

The mechanism proposed requires the initial formation of an iodonium cation which is then attacked by the azide ion.

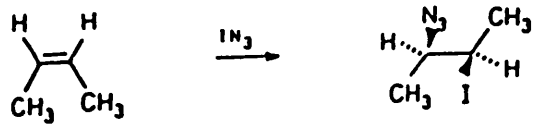


Iodine azide was first synthesised and isolated by Hantsch[93] in 1900 by stirring an aqueous suspension of silver azide in ether with iodine. From this suspension highly explosive yellow crystals of iodine azide were claimed to be isolated. However, this method was found to be unsuitable or the generation of the iodine azide as only black intractible oils that showed both hydroxyl and azido absorptions in the infra-red spectrum. These results indicated the decomposition of the iodine azide in the presence of water.

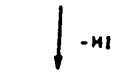
Hassner et al[90] found that when iodine monochloride is added to cold stirred slurry of sodium azide in acetonitrile, the dark colour of iodine monochloride is replaced with the yellow-orange of, presumably, iodine azide. Although this azide has never been isolated from these solutions, its presence can be inferred. If the inorganic salts are filtered off and an alkene is added to the clear yellow-orange solution, a high yield of an α,β - iodo-azide can be obtained, since sodium azide is essentially insoluble in acetonitrile. These results are incompatible with azide ion attacking a cation derived from iodine monochloride but are completely consistent with the existence of iodine azide in solution.

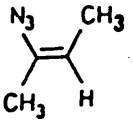
It was observed that the addition of iodine azide to alkenes was highly stereospecific. Thus the iodo-azide adducts of cis and trans - 2 - butene possess the threo - and erythro - 2 - azido - 3 - iodobutane structures, (176) and (178) respectively. The stereochemistry of these adducts was not directly obvious from their physical data, however, these isomers were formed cleanly and uncontaminated with each other. Insight on this point can be gained from a base catalysed trans elimination of hydrogen iodide from each isomer. In the case of the threo form the trans - vinyl azide (177) was produced, but the erythro isomer yielded only the cis structure (179), see schemes 28 and 29.

It would be expected that the azido group, because of a magnetic anisotropic effect, would deshield a cis orientated hydrogen atom and cause a downfield shift with respect to a trans hydrogen. This is shown by the downfield shift of the signal of the vinylic hydrogen by 0.43 ppm (the corresponding hydrogen in (179) absorbs at δ 4.7 ppm). The infra-red



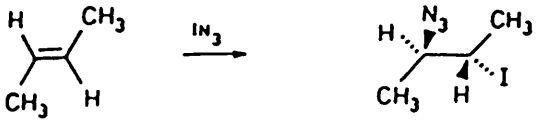
threo (176)



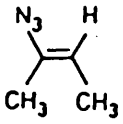


trans (177)

Scheme (28)

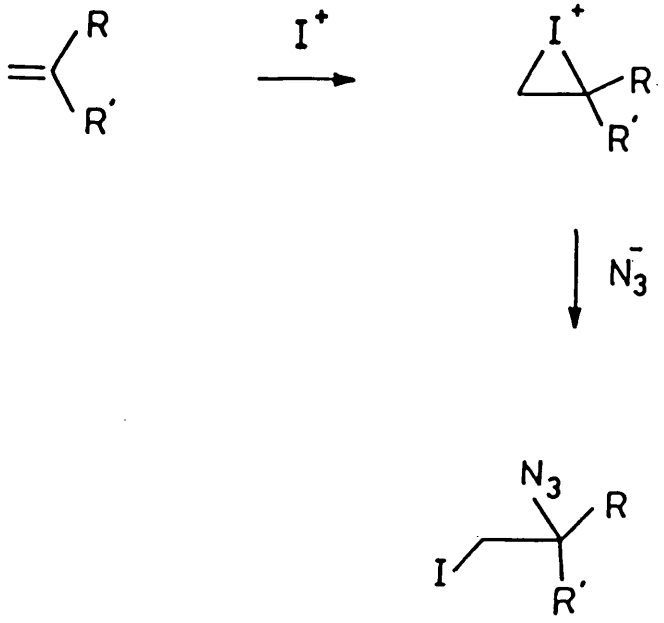


erythro (178)



cis (179)

Scheme (29)



(180) (181)

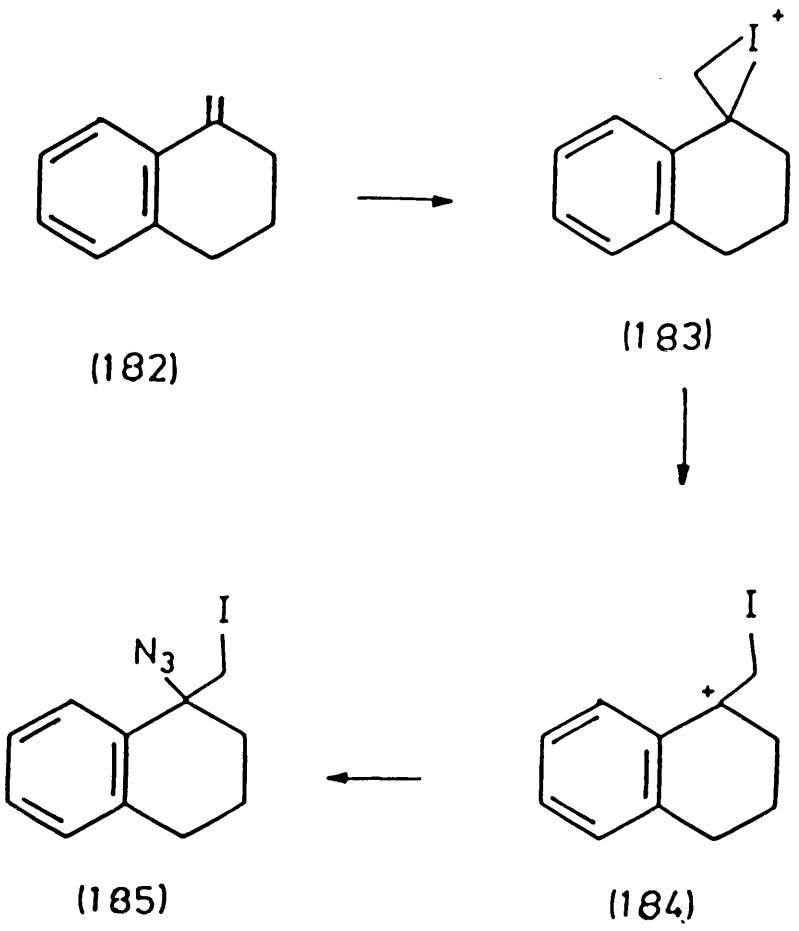
Scheme (30)

spectra of all iodoazides show a strong absorption at ν_{max} 2100 cm^{-1}, and the position of this band does not change appreciably in the spectra of the vinyl azides.

Iodine azide also adds stereospecifically to terminal alkenes to give an adduct which has the iodo function primary and where the azido function occupies the internal position. This fact follows from basic concepts concerning the relative stabilities of the two carbocations (180) and (181) in scheme 30.

The work in this research area consisted of the preparation of the spiro [2',1] - 1 ,2 .3 .4 -tetrahydronaphthylaziridine (173) shown in p123. This iodoazide was prepared by adding the alkene (182)[94] to a reacting mixture of iodine monochloride and sodium azide in dry acetonitrile. The reaction mixture was initially at methanol/ice bath (-4°C) and was gradually raised to room temperature. After the appropriate work up procedure, the resulting compound (185) was produced in 95% yield. The infra-red spectrum showed a characteristic azide group absorption band at 2120 cm^{-1}. The ^{1}H n.m.r. spectrum of this compound showed four aromatic proton signals at δ 7.0 -7.5 ppm. The two protons of the terminal methylene group were indicated as a singlet at δ 3.45 ppm. It was not clear whether this

methylene group was attached to the iodine atom or the azide group. However, since the carbonium (184) formed a stable entity, a primary iodo function is most likely to be formed than the primary azido function.

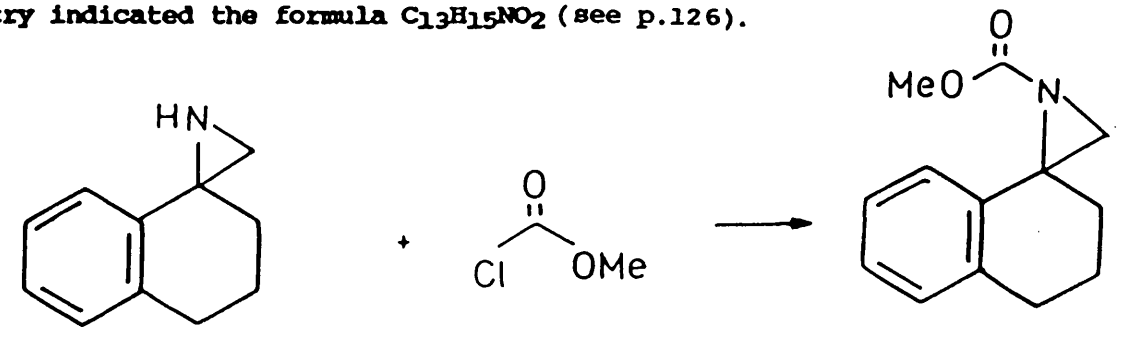


(182) (183) (184) (185)

The rest of the ^{1}H n.m.r. spectrum included the six aliphatic proton signals at δ 1.9 - 2.8 ppm.

The aziridine was subsequently prepared by reducing 1- azido -1 iodomethyl -1,2,3,4 - tetrahydronaphthalene (185) with lithium aluminium hydride ($LiAlH_4$). Excess $LiAlH_4$ was destroyed with 20% potassium sodium tartarate. Then quick filtrations gave the aziridine (173) in 60% yield. This aziridine was found to rapidly break down to a base line spot on tlc if the aqueous work up and drying procedures were prolonged. The base line spot

had an infra-red spectrum similar to that given by the aminoalcohol (145), described in chapter two page 95 . Further breakdown was also caused during the separation process using alumina column chromatography. However, some of the pure aziridine can be obtained if a fast column chromatography technique was carried out. Once pure it was stored at 0° under dry nitrogen for a few days. The infra-red spectrum showed a weak absorption due to the aziridine -NH function at ν3300 cm^{-1}. The ^1H n.m.r. spectrum of this compound gave the following signals: δ 6.8 - 7.2 ppm as a multiplet corresponding to four aromatic protons; δ 2.8 - 3.0 ppm, a complex spin system, was due to two protons of the aziridine - CH_2 group; δ 2.0 - 2.05 ppm a multiplet which could be deutrated, was due to the -NH group and δ 1.4 - 2.0 ppm of another multiplet was due to the three methylene groups.Further structural proof of the aziridine (173) was obtained when a more stable derivative was synthesised. This derivative was the N- methyl carbamate of the spiro aziridine and was prepared by reacting the aziridine with methyl chloroformate in triethylamine. Separation of the resulting product was achieved on an alumina column to yield 40% of the pure derivative (186). The infra-red spectrum indicated an amino absorption at ν_{max} 3340 cm^{-1} and a carbamate at ν_{max} 1700 cm^{-1}. High resolution mass spectrometry indicated the formula $C_{13}H_{15}NO_2$ (see p.126).

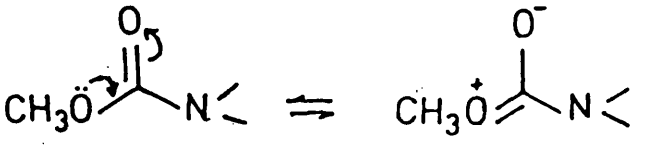


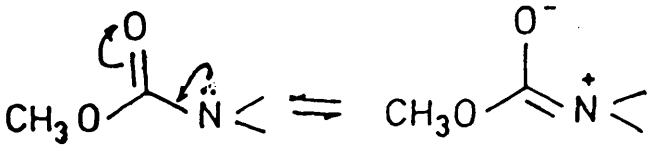
(186)

2.3.2.2. Chemical behaviour of the aziridine

The synthesis of the crude aziridine as discussed previously was easily

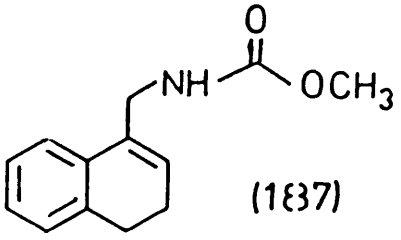
achieved. However, its purification has presented a serious problem due to its rapid hydrolysis on contact with atomospheric moisture giving the amino alcohol. An attempt was made to "protect" the aziridine by N-carbamoylation, since now conjugation of the carbamyl group with non-bonded pair of electrons on the nitrogen atom might reduce its basicity and hence propensity to undergo protonation and hydrolysis.





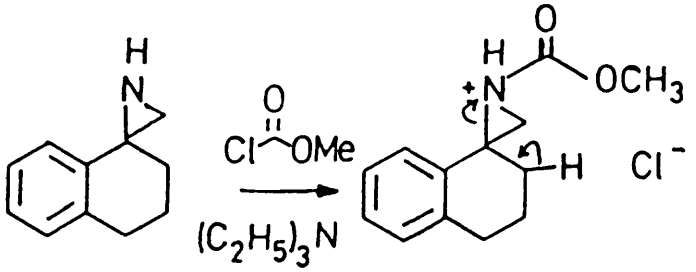
The pure aziridine (0.01g) was added to dry triethylamine ($10cm^3$) in a sealed flask under nitrogen at 0 C. One equivalent of methylchloroformate was syringed in slowly. The crude product was then columned on alumina using ether/60-80° petroleum ether to give the assumed carbamate (186) in 40% yield (0.005g). High resolution mass spectrometric measurement showed a molecular formula $C_{13}H_{15}NO_2$ in line with the desired structure, whereas a ^1H n.m.r. (400MHz) indicated that this assignment was untenable. Thus an unexpected triplet signal was observed in the olefinic region at 6.03 ppm (J=4Hz). Four aromatic protons rosonated at δ 7.00-7.25 ppm as a multiplet. A broad, weak singlet at δ 4.72 ppm [exchangeable (D_2O shake] was assigned to -NH proton resonance and a broad doublet at 4.2 ppm (J=5Hz) corresponds to the resonance of two methylene protons. The chemical shift position of this signal and the fact that when the compound was shaken with

deuterium oxide this signal "sharpened"indicates this methylene group to be adjacent to the -NH function. A sharp singlet at δ 3.6 ppm due to three protons may be ascribed to the resonance of the methoxy protons. Finally a multiplet at δ 2.2 ppm and sharply defined triplet at δ 2.75 ppm (J=8Hz) both signals integrating to two protons suggest the presence of a $=CH-CH_2CH_2$ Ar group. From this evidence the structure for the new compound was revised to that of the carbamate (187).

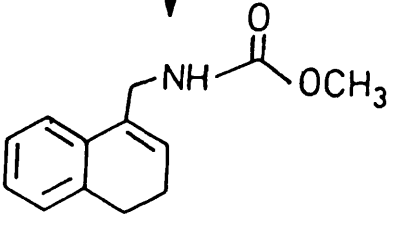


(187)

It is suggested that during the formation of the N-protected aziridine, the intermediate (188) was first produced, but this then ring opened to afford (189).



(188)

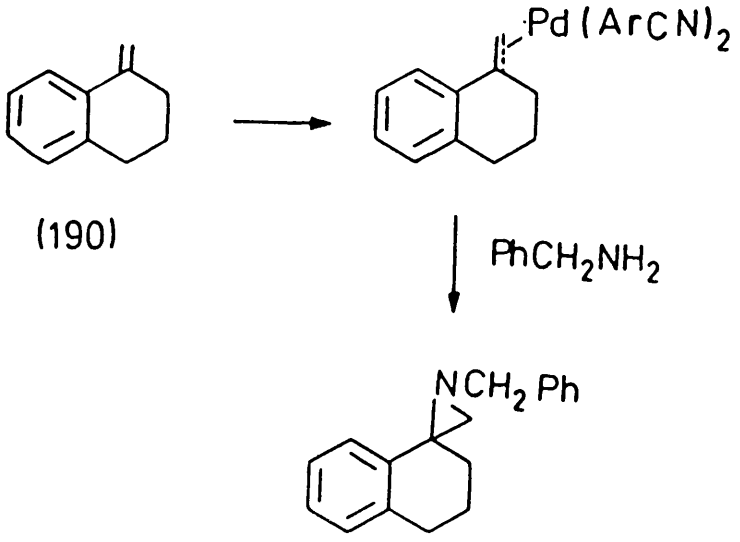


(189)

A series of experiments were then attempted to ascertain if N-alkyl derivatives might be prepared from the aziridine by reaction with alkyl halides. Unfortunately these all failed. Base was not added during these reactions since the aziridine was assumed to be susceptible to base promoted ring opening, but of course should the N-alkylation proceed acid would be liberated which is also deterimental. In an attempt to alkylate the N-atom of the aziridine by reaction with carbenes it was combined with ethyl diazoacetate and palladium(II)acetate. This also led to decomposition of the heterocycle but no tangible products were obtained.

Protected aziridine via exomethyline tetrahydronapthalene

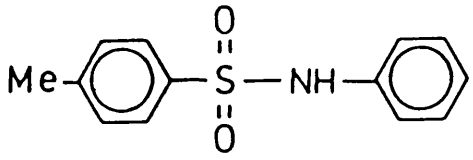
It is known that alkenes form palladium complexes[101] which then may be reacted with amines to yield aziridines. Thus the N-alkylated aziridine (191) might be obtained from the alkene (190) by reaction first with bis(benzonitrile) palladium dichloride and then with benzylamine. In practice no reaction occurred.



(190)

(191)

A final attempt to produce an N-substituted aziridine involved a reaction between the alkene (190) and tosylazide in benzene solution. Irradiation of the mixture only produced the sulphonamide (192). The intermediate nitrene simply reacted with the solvent. When cyclohexane was used in



(192)

place of benzene the result was much the same and only the sulphonamide was isolated. Related reactions in other solvents (chlorobenzene and nitrobenzene) gave no products at all.

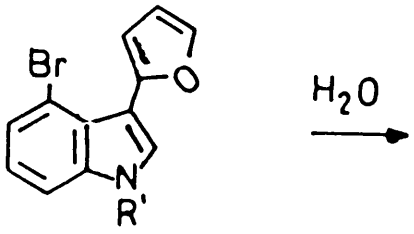
CHAPTER FOUR

ALTERNATIVE APPROACH TO ERGOT ALKALOIDS

2.4.1 INTRODUCTION

In previous chapters of this thesis attempts to rearrange the aziridine (173), see p.117, into a precursor of the ergot alkaloids have been described. None of these have been successful and so in the concluding chapter we report on a more traditional approach towards the natural products. Here the starting material was the bromofuranylindole (193), which on hydrolysis should yield the aldehyde (194). The latter compound is a vinylogous amide and on base treatment would then undergo aryne formation with concomitant deprotonation at the methylene group adjacent to the aldehyde function. Ring closure of the product (194) would then give the tricyclic compound (195) which is appropriately functionalized to allow further modifications on towards the ergot tetracyclic system (p.132)

Scheme 31



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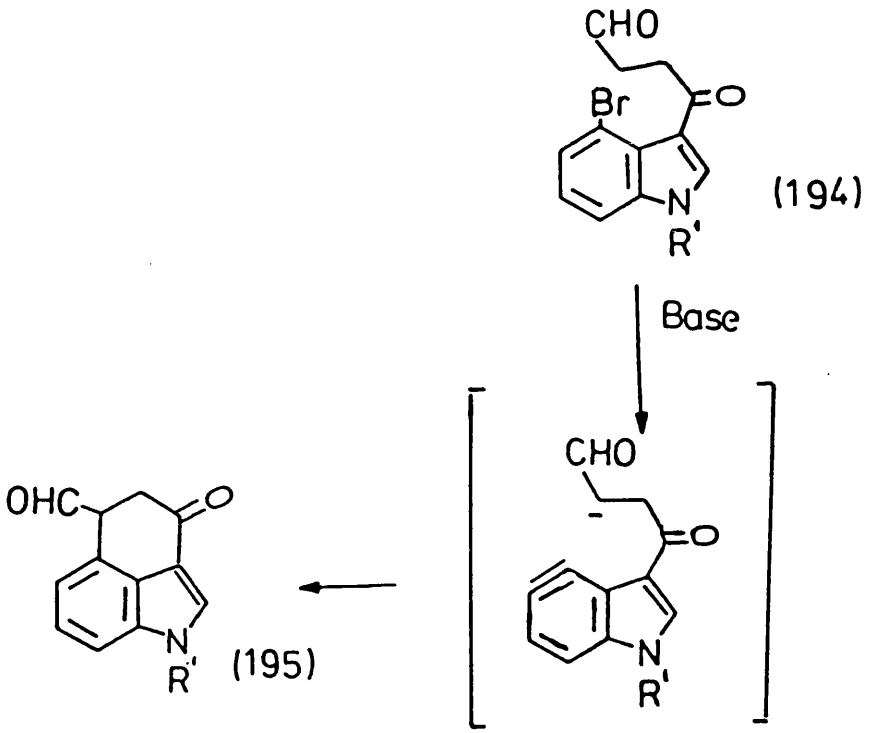
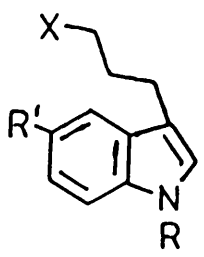


Similar cyclisations using 3-butyl-indoles (196) and -indolines (197) were studied some years ago by Julia et al[25][113] (see p. 34). The best yields obtained by the French workers, for the amide ($X=CONEt_2$) was, however, only 20%. Nevertheless, this model chemistry was later incorporated into a full synthesis of lysergic acid diethylamide.



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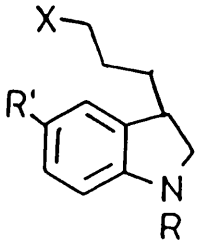
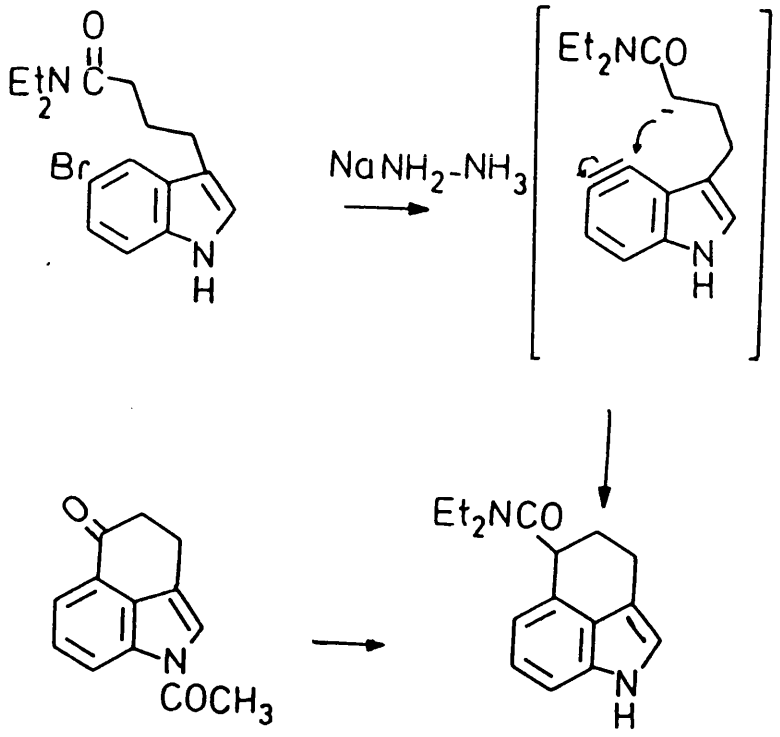


(197)

$X = CONEt_2$

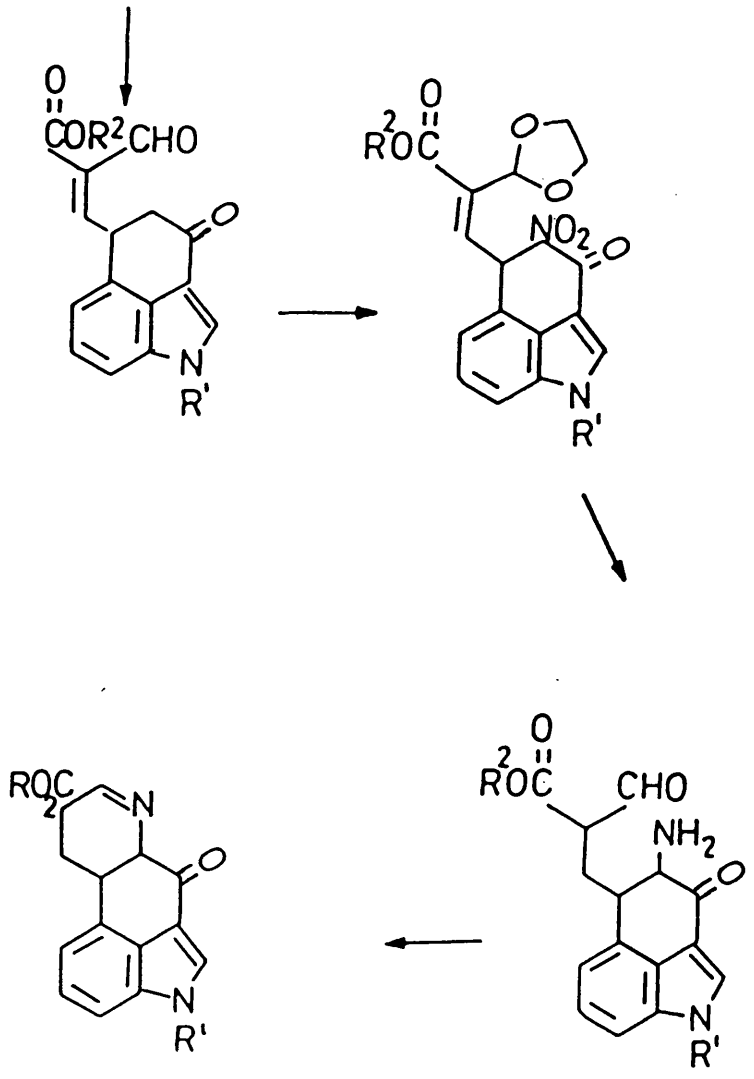
$R' = Br$



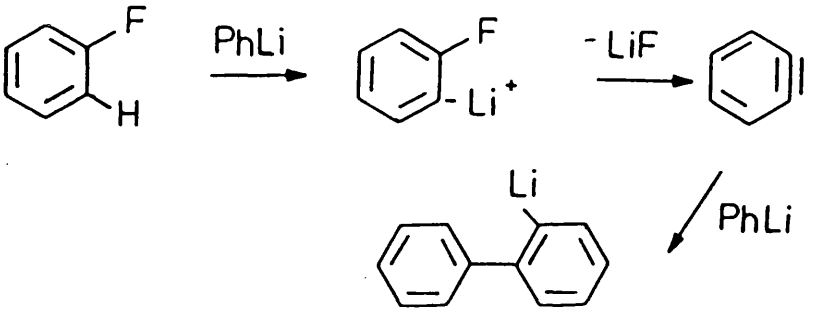
scheme (32)

In our study we hoped to obtain higher yields for the production of the tricyclic structure (195), and sought chemical precedence for the elaboration of the fourth ring. This is forthcoming, for example:

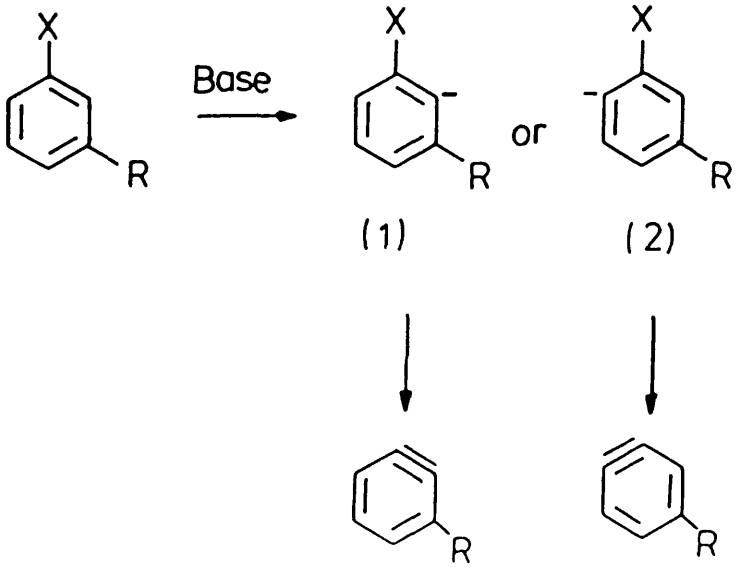
(195)



Wittig[32] was the first to suggest the presence of arynes through his studies of halogenobenzenes reaction with phenyl-lithium to produce biphenyl:

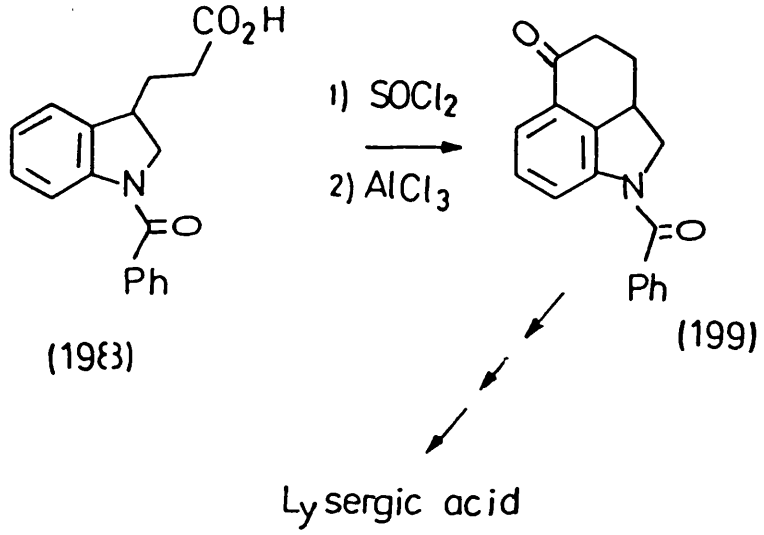


In many systems two different arynes are possible meta-substituted halogenobenzenes are the simplest examples, others include 2-halogenonaphthalenes and 3-halogenopyridines.

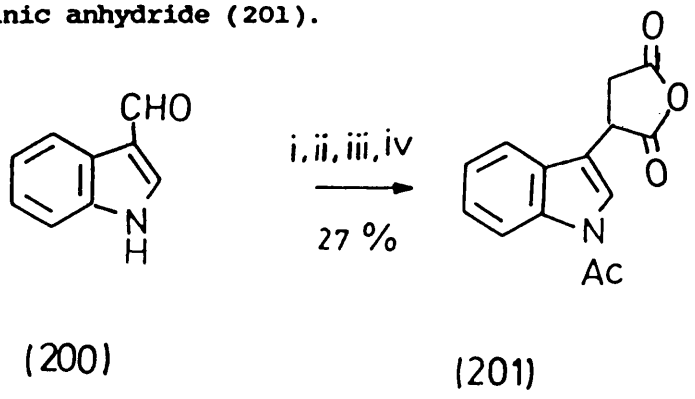


The effect of the substituent R in determining the ratio of the two arynes in an inductive one. If R is inductively electron withdrawing, the anion [1] will be formed in preference to [2] and vice-versa.

The work of Kornfeld (see p. 28) who used an internal Friedel-Craft's cyclisation of the acid (198) to give the tricylic ketone (199), which then became starting compound for an early ergotamine synthesis.



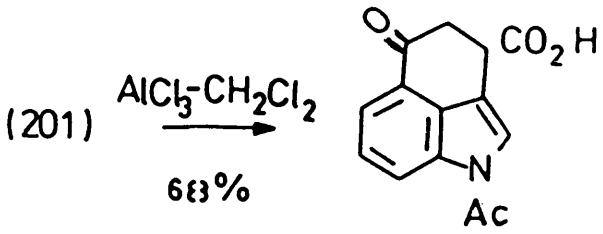
Another illustration is provided by the work of Szmuszkovicz[105] who in 1964 affected the synthesis of the ketoacid (202) by rearrangement of the indolylsuccinic anhydride (201).



Reagents: i) $CH_2(CN)CO_2Et$ - piperidine;

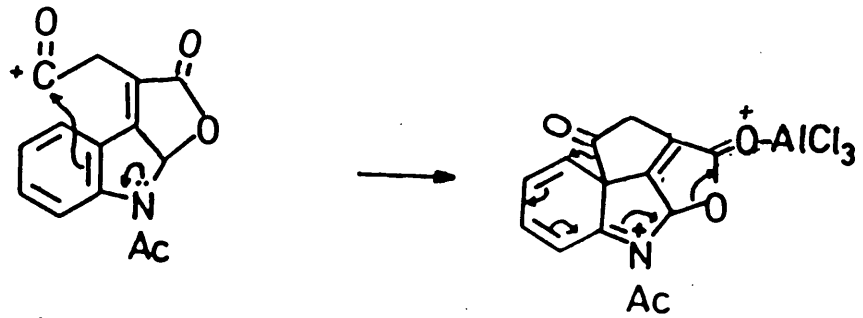
ii) KCN-EtOH; iii) KOH-H_2O-ΔH;

iv) $H_3C-\overset{OAc}{\overset{|}{C}}=CH_2-H^+$, then AcOH-$Ac_2O$

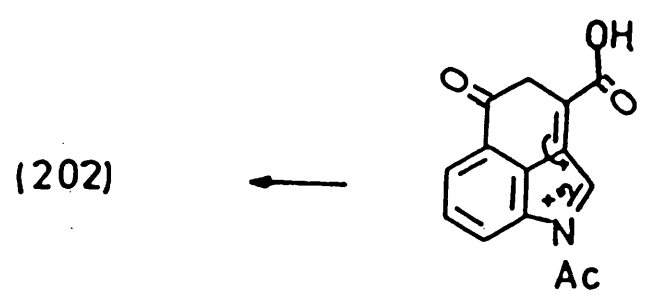


(202)

The mechanism[104] given shows the formation of the intermediate (203) in which the indole 2,3-double bond may be protected. The acylating species may then be orientated towards the 3a-position. The strain free intermediate (204) may then undergo a [1,2] sigmatropic shift to the 4-position to give (205):

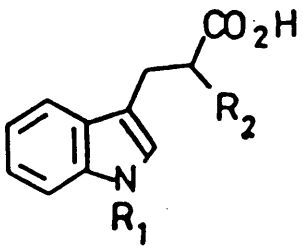


(203) (204)



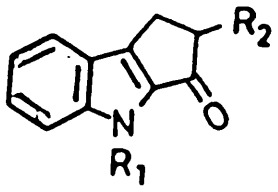
(205)

By 1980 Szmuskovicz method appeared to be the only recorded example of an indole with unsubstituted 2-position undergoing the Friedel-Crafts reaction in the 4-position. In general, nucleophilic activity of 2-position of indole is very dominant. For example, cyclization of indole-3-ylpropionic acid (206) takes place at the 2-position to give 3-oxo-1,2,3,4-tetrahydrocyclopent-[b]indole (208). Cyclization of (207) at 4-position may be due to the decreased nucleophilicityof 2-position by the N-acetyl group. However when Nagasaka and Ohki[117] chose 3-(1-acetylindol-3-yl) propionic acid (207) as the most simple model compound, they found that synthesis of (207) was difficult.



(206) $R_1 = R_2 = H$

(207) $R_1 = COCH_3$, R_2



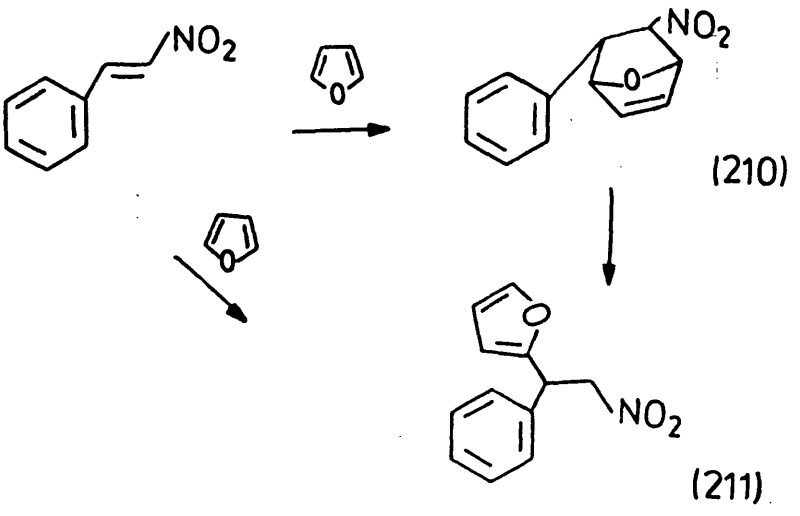
(208) $R_1 = R_2 = H$

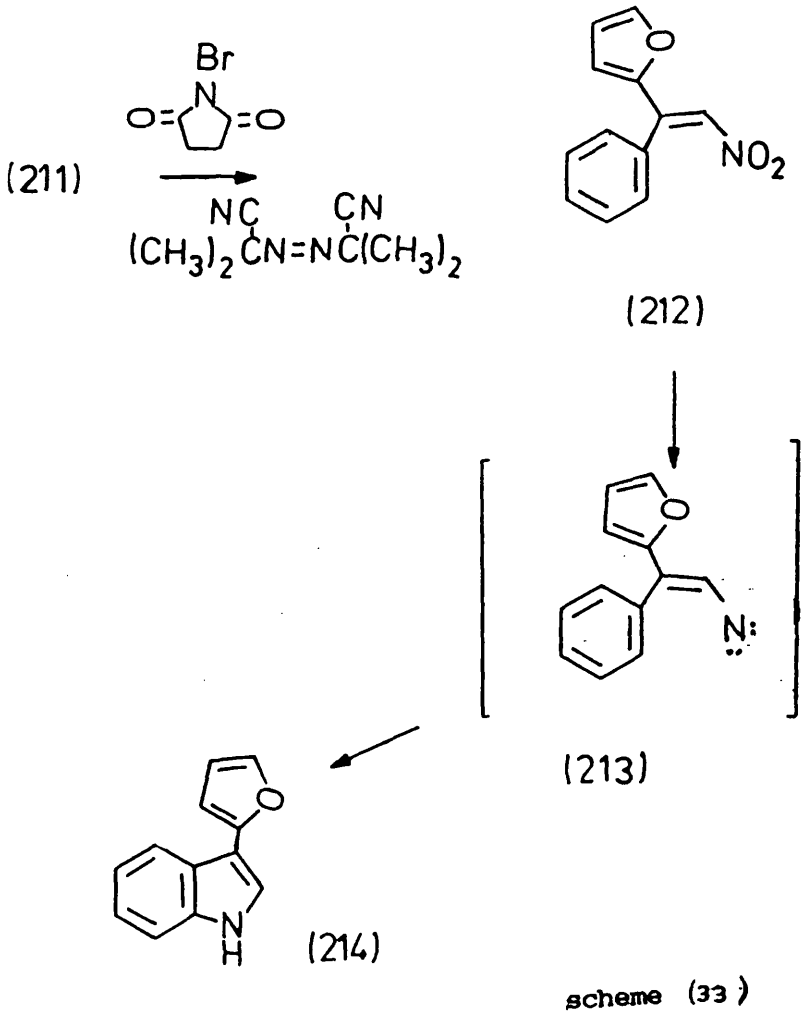
(209) $R_1 = COCH_3, R_2 = H$

Eventually they made (207) by esterification of (206) with tert-butanol and trifluoracetic anhydride in dry benzene, acetylated this tert-butyl ester with NaH ,CH_3COCl/DMF (dimethylformiamide) and hydrolysed this ester with trifluoroacetic acid to give (207) in 41% yield. The Friedel-Crafts reaction of the acid chloride of (207) gave (209) as a sole product in 60% yield. Therefore cyclization of 1-acetylindol-3-yl alkanoic acid by the Friedel-Crafts reaction occurs at 2-position in general. Cyclization of (207) at 4-position was regarded as a unique example.

2.4.2 DISCUSSION

Earlier work in this department has shown that when nitrostyrene is reacted with furan in the presence of the Lewis acid zinc iodide the product is not the Diels-Alder adduct (210) but rather the 2-substituted furan (211). There is a possibility that the adduct (210) is converted under the reaction conditions into (211). This product can be dehydrogenated in two steps (bromination, followed by dehydrobromonation) to the styrene (212). Reaction of this compound with triethylphosphite then affords the furanylindole possibly through the intermediacy of a nitrene (213). See scheme 33.


NO2
O
NO2
O
(210)
O
NO2
(211)


Br
N
O=
=O
(211)
NC
CN
(CH3)2CN=NC(CH3)2
O
NO2
(212)
O
N:
(213)
O
N
H
(214)

scheme (33)

We decided to repeat this synthesis and to investigate the hydrolysis of the product first before preparing the bromo derivative. In doing so we noted that the product (214) was both air and light sensitive and that the final step in the sequence was unpredictable giving yields ranging from 20-50% depending it seems on how rapidly the reaction mixture is worked up.

2.4.2.1 Reactions of 3-[2-furanyl]indole

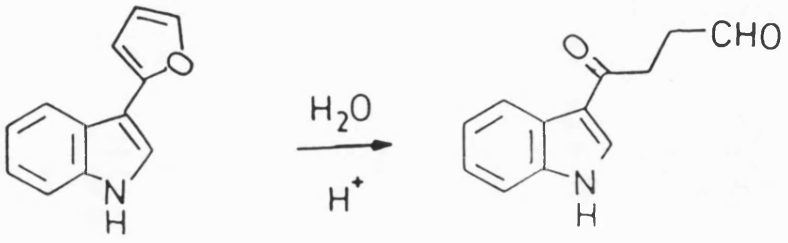
After a good deal of trial and error it was discovered that hydrolysis of the furanyl compound (214) was best achieved by treatment with a mixture of 75% acetic acid and a drop of concentrated sulphuric[110,111] acid after stirring for 2 hours at room temperature and TLC analysis showed a more polar component (R_f=0.7[100% EtOAc]) to be present. Instead of the expected molecular ion m/z 201 for the aldehyde (216), the new product exhibits M^+ m/z 366 (corresponds to the molecular ion formed by the loss of water from the parent molecule of m/z 384).

The high resolution mass spectrometry measurement gave 366.1348 for $C_{24}H_{18}N_2O_2$ requiring 366.1366 and hence confirming this molecular ion.

In the infra red spectrum both hydroxyl and amino bands are present (3460 and 3260cm^{-1}) together with a carbonyl band at 1650cm^{-1}. Three proton resonances in the ^1H n.m.r. spectrum (δ11.93, 11.29 and δ4.9ppm, all broad singlets) disappear when the sample is shaken with deuterium oxide. The low chemical shift of the first two of these signals suggest that they are associated with indolic-NH groups, whreas that at δ4.9 is likely to be the resonance of a hydroxyl group.

There are ten proton resonances within the range δ7.0–8.39, two of which resonant as doublets in the undeuterated sample but revert to singlets after the exchange of the -NH protons has occurred. These signals at δ8.39 and δ7.57 are indicative of the presence of two β-substituted indole units and arise from the signlas of the α-protons. One of these indole units must contain a deshielding feature, however, in order to account for the low field nature of the δ8.39 resonance. Two resonances at δ6.4 and δ6.2 form an AB spin-spin pattern with J_{AB}=3Hz. These signify that a 2,5-disubstituted furan ring system is probably present. Leaving an eight proton multiplet between δ7.0–8.3 as evidence for the remaining aromatic resonances of the two indole nuclei. Finally there are five aliphatic proton signals between δ3.8 and 3.3ppm which on detailed inspection indicate the possibility of a $CH(OH)CH_2CH_2CO$ bridging unit. This is confirmed by the ^{13}C n.m.r. spectrum which shows multiplities and chemical shifts compatible with this type of grouping and also supports the analysis of structure for the heterocyclic part of the molecule.

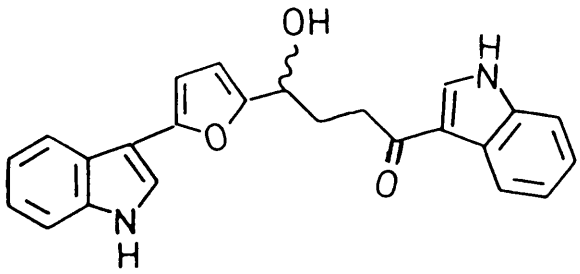
It is clear therefore that the new product has structure (217). This suggests that the required aldehyde (216) is indeed formed under the reaction conditions, but that it then rapidly reacts with more starting material to afford the observed compound (217).



(215) (216)

(216)

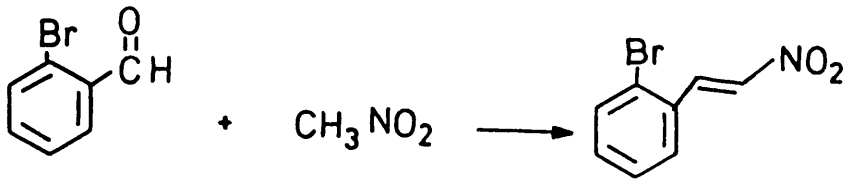
↓ (215)



(217)

We next undertook a series of reactions designed to prevent the aldehyde reacting with the parent furanylindole. However, all of these were unsuccessful leading simply to diminished yields of the alcohol (217) and/or tar formation.

This was a very disappointing conclusion to our efforts since in parallel with this work we had already begun the synthesis of bromoanalogue 2-Bromobenzaldehyde was reacted with nitromethane in the presence of sodium hydroxide to give the nitrostyrene (219), plus a substantial amount of its precursor (218). This can be readily dehydrated to (219) by treatment with acetic anhydride and pyridine at 100°C. The nitrostyrene was then reacted with furan in the presence of zinc iodide catalyst to yield the compound (220), but in view of the results described above the remaining steps on to the bromofuranyl indole were not attempted.



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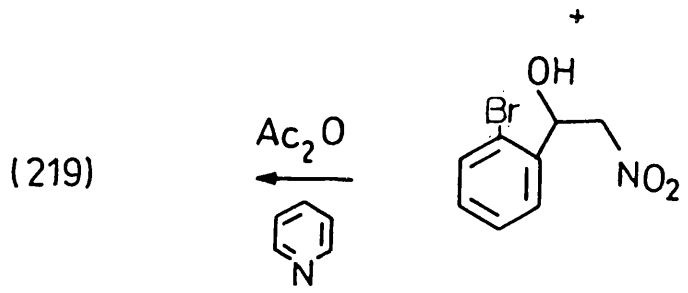
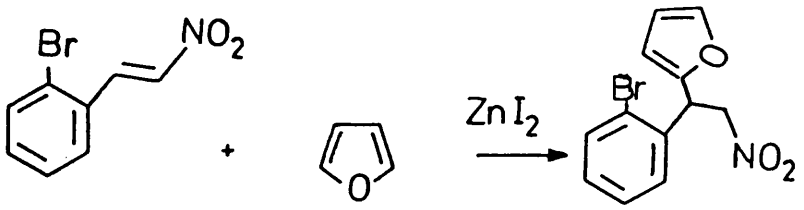


(218)



(220)

EXPERIMENTAL

GENERAL

Melting points were recorded on an Electro-thermal MK II apparatus and are uncorrected. Infra-red spectra were recorded on Perkin-Elmer 197 or 1310 grating spectophotometers as nujol or thin film. Ultra-violet spectra were recorded on Perkin-Elmer 402 and Lambda 3 instruments in ethanol solution. ^{1}H NMR spectra were run at 60 MHz on Perkin-Elmer R24B and Varian EM360 spectrometers; at 100 MHz on a Jeol PS100 spectrometer; and at 400 MHz using the SERC facility at Warwick University. Mass spectra and high resolution accurate mass measurements were determined on a VG 7070E instrument with VG2000 data system.

Reactions were monitored by tlc on Merck DC Alufolien plates coated with Kieselgel $60F_{254}$ or Merck DC Alufolien alumina oxide $60F_{254}$ using appropriate solvent system. Column chromatography was carried out using short path pressurised columns packed with Merck 7747 silica gel, and the solvent was eluted under pressure provided by hand bellows. Alumina column chromatography was packed with Beckmann type 1, neutral (pH 6.5-7.5). Ethyl acetate and petroleum ether 60-80° were distilled prior to use.

THF was dried by distillation from sodium/benzophenone ketyl. Diethyl ether was dried by standing over sodium wire for at least 24 hours. Dichloromethane was dried by distillation from calcium hydride, and acetonitrile was dried distilled over phosphorous pentaoxide.

Unless otherwise stated, all other solvents and reagents were used as provided.

Molar quantities of substances are represented as M for mole or mM for millimole.

1-(Cyclohex-2-enyl)ethylideneaniline(9)

Acetylcyclohexene (1.24g, 0.01M) and aniline (0.93g, 0.01M) in dry benzene ($50cm^3$) containing Amberlyst R-15 resin (1g) were heated under reflux for three days. The solvent was then removed under reduced pressure and the residue chromatographed on silica using diethyl ether/60-80°C petroleum ether (1:2) as eluant to give the title compound as a gum (0.46g, 23%); ν_{max} 2920, 1620, 1600, 1480, 1220, $700cm^{-1}$; $\delta_H(CDCl_3)$, 7.3-6.6(5H,m, aromatics), 6.51(1H,t, J=2Hz, vinylic proton), 2.46-2.20(4H,m), 1.89(3H,s, CCH_3), 1.35(4H,m); m/z M^+ 199.1351, $C_{14}H_{17}N$ requires 199.1357.

1-(Cyclohex-2-enyl)ethylidene-4-methoxyaniline(10)

Acetylcyclohexene (1.24g, 0.01M) and 4-methoxyaniline (1.23g, 0.01M) in toluene ($50cm^3$) containing Amberlyst R-15 resin were heated under reflux for three days and the solvent was then removed under reduced pressure. The residue was then chromatographed on silica using diethyl ether/60-80° petrol (1:1) as eluant to give the title compound as a colourless solid (0.46g, 20%), m.p. 46-47°C; ν_{max} 1640, 1220, $820cm^{-1}$; $\delta_H(CDCl_3)$ 6.92(2H,2xd, J=9Hz), 6.40(2H, 2xd, J=8Hz), 6.5(1H,m,vinylic proton),3.79(3H,s,OCH_3), 2.4(2H,m), 2.24(2H,m), 1.93(3H,s,CCH_3), 1.7(4H,m); m/z 229.1461 $C_{14}H_{19}NO$ requires: 229.1462. Attempts to obtain satisfactory elemental analyses for the compound failed because of its instability.

A rather unstable side product from this reaction the amino alcohol (13) [see p.12] was also produced ν_{max} 3600, 3500, 2950, 1500 cm^{-1}; m/z 247.

N-Benzylideneaniline(14)[103]

Benzaldehyde (1.1g, 0.01M) and aniline (0.9g, 0.01M) in dry benzene (50cm^3) containing glacial acetic acid (1 drop) were heated together in a Dean-Stark apparatus for 2$^1/_2$ hrs. The solvent was then removed and the residue crystallised from methanol to give the title compound as almost colourless prisms (1.7g, 47.5%), m.p. 45-47° (lit., 48°) ν_{max}(Nujol) 1610cm^{-1}; m/z 181, [Found: C, 86.1; H, 5.9; N, 7.6 calculated for $C_{13}H_{11}N$ C86.2; H, 6.1; N, 7.7 %].

Phenanthridine(17)

A mixture of N-benzylideneaniline (0.3g, 1.7mM), acetonitrile (10cm^3) and palladium acetate (0.2g, 0.8mM) was placed in a pressure tube and sealed under a nitrogen atmosphere. This was then placed in a hot oil bath (220°C) behind a safety screen for one day. The solvent was then removed in vacuo and the dark brown residue chromatographed on an alumina column using ether/60-80°C petroleum ether (1:1) as eluant. Early fractions contained a single component, these were decolourised over charcoal, evaporated and the residue allowed to crystallize. Colourless needles of phenanthridine were obtained (0.009g, 3%) m.p. and mixed m.p. (with an authentic specimen) 104°C (lit. 104°C)[27].

Photochemical reaction of 1-cyclohex-2-enyl)ethylideneaniline(9) and 1-(cyclohex-2-enyl)ethylidene-4-methoxy aniline(10)

The imine (9) (0.10g, 0.5mM) was placed in a photochemical reactor containing dry benzene (500cm^3) and protected by a nitrogen gas atmosphere. One equivalent of iodine (0.06g) was also added. The mixture was irradiated with a Hanovia low pressure lamp (16W). The reaction progress was monitored using tlc every $^1/_2$ hr. A streak developed on the plates shortly after the commencement of irradiation, and the reaction was stopped after a period of 7 hrs. No product isolation was attempted due to the complexity of the resulting mixture.

The above reaction was repeated without the addition of iodine but no change to the starting material occurred.

Photochemical experiments using the imine (10) were equally unproductive.

Other photochemical reactions with 1-(cyclohex-2-enyl)ethylidene-4-methoxyaniline

1-(Cyclohex-2-enyl)ethylidene-4-methoxyaniline (10) (0.1g, 0.5mM) dissolved in dry cyclohexane (150cm^3) and placed in a quartz tube placed in a carousel. One equivalent of trifluoroacetic acid (TFA) was added. The tube was sealed with a septum under nitrogen and irradiated with a Hanovia low pressure lamp (16W) for 24 hrs. The reaction mixture was washed with 2N sodium bicarbonate solution to neutralise excess acid, the organic layer separated, dried over $MgSO_4$ and the solvent removed in vacuo. The resultant oil showed no absorption bands in the infra-red due to the starting

imine but the characteristic carbonyl absorption of acetylcyclohexene was present. This indicated the breakdown of the imine (10) to its parent components.

Iron complex of N-Benzylideneaniline(19)

Enneacarbonylidi-iron (0.3g, 0.9mM) was added to N-benzylideneaniline (0.5g, 2.7mM) in dry benzene under nitrogen atmosphere. The reaction mixture was placed in a cold bath and then the temperature was raised slowly to room temperature.

A period of 3 days was allowed for the reaction to reach completion, then the solvent was removed in vacuo and the crude product was chromatographed on a short alumina column ether/60-80°C petroleum ether as eluant. The product obtained as pink crystals was stored under nitrogen, it has m.p. 50-51°C. The infra-red spectrum exhibits four carbonyls vibrational bands at 2075, 2040, 1995 and 1945 cm^{-1}. Unfortunately this compound is very unstable and no further data was obtained.

Iron complex of 1-(cyclohex-2-enyl)ethylidene-aniline(18)

Enneacarbonyldi-iron (0.2g, 0.5mM) was added to a solution of the imine (9) (0.3g, 1.5mM) in dry benzene ($40cm^3$). The reaction was placed in a cold bath (0°C) and protected by nitrogen atmosphere. It was observed that no change to the starting material had occurred after a period of 6 hrs. A

condensor was then connected to the reaction flask and gentle heating (40°C) was applied for 2 days. After this time a new spot was seen on tlc analysis and the reaction was worked up in the following manner:
The solvent was removed under reduced pressure and a red oily product was obtained which was chromatographed very quickly over a short alumina column with diethyl ether/60-80°C petroleum ether (2:1) as eluant. The product was a red oil, which showed four carbonyl vibrational bonds in its infra-red spectrum at 2050, 2025, 1983 and 1962cm^{-1} which are characteristic of complexes of this type.[15] Mass spectrometric fragmentation of this complex was difficult to interpret and complete decomposition occurred within a short time even though the compound was protected by nitrogen and kept at low temperature.

3,4-Dihydro-1(2H)-N-phenylnaphthylimine(88)[42]

α-Tetralone (2g,14mM), aniline (1.3,14mM) and a crystal of p-toluenesulphonic acid were dissolved in benzene and heated at reflux in a Dean Stark apparatus. After no more water was collected the solvent was removed and the crude product chromatographed on silica eluting with 20% diethylether in 60-80° petrol. This gave the known compound as a pale yellow solid, m.p. 62-64°C (lit, 63-64°) (1.8g, 60%). ν_{max}(Nujol) 1630, 1600, 1220cm^{-1}; δ_H ($CDCl_3$) 8.5-6.8(9H,m), 2.9(2H,t, J=7Hz,-CH_2), 2.55(2H,t, J=6Hz,-CH_2). 2.0-1.9(2H, m-CH_2); m/z 221.1204, calculated for $C_{16}H_{15}N$ 221.1216.

Preparation of zinc-copper couple[38,39] and its reaction with the imine (88) in the presence of di-iodomethane.

Zinc powder (16.4g, 0.25M) was washed with

a. 3% hydrochloric acid (4x0.15cm^3)

b. distilled water (4x0.18cm^3)

c. aqueous copper sulphate (2%, 2x50cm^3)

d. distilled water (2x30cm^3)

e. absolute ethanol (2x15cm^3)

f. absolute ether (2.5x25cm^3)

The product reagent (0.13g,0.002M) then reacted with the imine (88) (0.88g, 0.004M) in the presence of di-iodomethane (0.8g, 0.003M). The reaction flask being covered with foil to exclude light. After 2 days at reflux the dark coloured reaction mixture was treated with aq. sodium bicarbonate and then extracted with dichloromethane. No new product was obtained although some starting material was recovered.

Attempted reaction of the naphthylimine(88) with carbenes

(a) Reaction of dichlorocarbene with 3,4-dihydro-1(2H)-N-phenyl-naphthylimine

Dry ether (50cm^3), Analar dry chloroform (10cm^3) and 3,4-dihydro-1(2H)-N-phenylnapthylimine (0.1g, 0.45mM) were mixed together and protected under a nitrogen atmosphere. Freshly sublimed potassium t-butoxide was then introduced. No change was indicated on tlc analysis after 15 minutes at 0^{o}C so the reaction mixture was allowed to warm to room temperature and then it was heated at reflux for 1 hr. No reaction was observed.

(b) Reaction of the imine(88) with dichlorocarbene in the presence of a phase-transfer catalyst

Powdered sodium hydroxide (0.85g, 0.02M) was placed in a dry flask containing dry Analar chloroform (80cm^3) protected by a septum. The imine (88) (0.94g, 4.3mM) was then added using a syringe through the septum, followed by a catalytic amount of cetyl triethyl ammonium bromide. the mixture was then placed in an ultrasonic bath for 6 hrs. Once again tlc analysis showed no apparent change to the starting material.

2-Ethoxymethylene-3,4-dihydro-1(2H)-N-phenylnaphthylimine(103)

The imine (88, R=Ph) (0.44g,19mM) was added to a suspension of powdered sodium hydroxide (0.08g,20mM) in dry chloroform (20cm^3) and the reaction mixture, protected by an atmosphere of nitrogen, was placed in an ultrasonic bath.

After 4 days the solvent was removed and the residue extracted with diethyl ether and chromatographed on silica eluting with 30% diethyl ether in 60-80°C petrol. This gave the title compound as a colourless solid, m.p. 82-84°C,(0.05g, 10%); ν_{max}(Nujol) 1640, 1600, 1220cm^{-1}; δ_H($CDCl_3$), 7.2-6.8(9H,m), 5.9(1H,t,J=5Hz), 4.45(2H,q,J=6Hz), 2.60(2H,t,J=7Hz), 2.2-2.1(2H,m), 1.45(3H,t,J=6Hz), [Found: C, 82.2; H,6.9; N,5.25 $C_{19}H_{19}NO$ requires: C,82.2; H,6.9; N, 5.1%].

Attempted reactions of ethylchloroacetate with 3,4-Dihydro-1(2H)-N-phenyl naphthylimine (88)

(a) Ethylchloroacetate (0.56g, 4.5mM) was added slowly to a molecular equivalent of sodium hydride (0.1g, 99%) in anhydrous benzene (50cm^3). When the evolution of hydrogen gas stopped, the imine(88) (1g, 4.5mM) in benzene (10cm^3) was syringed into the reaction vessel. Tlc analysis showed no change to starting imine even after 24hrs and a period of heating at reflux.

(b) The above reaction was repeated but with excesses of ethylchloroacetate and sodium hydride. Starting material was still recovered unchanged.

Attempted reaction of diazomethane with 3,4-dihydro-1(2H)-N- phenylnaphthylimine

Diazomethane was generated using the following method: N-nitroso-p-toluene sulfonamide (diazald) (1.4g, 6.7mM) in ether (10cm^3) was placed in the dropping funnel of a diazomethane generating kit supplied by Aldrich. Diazald[102] was added dropwise to a flask containing a mixture of aqueous potassium hydroxide (6g/10cm^3), ethanol (10cm^3) and ether (10cm^3) placed in hot water bath (60^{o}C). A yellow gas (CH_2N_2) was libertaed and condensed directly into a cold flask containing 3,4-dihydro-1(2H)-N-phenylnaphthylimine (88) (0.5g, 2.2mM) in ether (10cm^3). Stirring was started at 0^{o}C for 4 hrs but tlc analysis indicated no change to the starting imine. Stirring was continued at room temperature for 2 days but still there was no sign of reaction.

Attempted photoreaction of diazomethane with 3,4-dihydro-1(2H)-N-phenyl-naphtylimine

Excess diazomethane was generated using method desribed on page 152 and added to a solution of 3,4-dihydro-1(2H)-N-phenylnaphthylimine(88) (0.5g, 2.2mM) in dry ether (150cm^3) contained in a quartz tube. The reaction mixture was then irradiated with UV light using a Hanovia low pressure lamp (16W), but despite a prolonged exposure to the light source (24hr) no change was observed and on work up only starting imine was recovered.

Spiro-[1,2,3,4-tetrahydronaphthalene-1-4'-(-3'-α and β-ethoxy-1'-phenyl--azacyclobutan-2'-ones)] (91) and (90).

3,4-Dihydro-1(2H)-N-phenyl-naphthylimine (0.5g,2.2mM) in benzene (500cm^3) containing ethyl diazoacetate (0.83g,7.2mM) was protected by a nitrogen atmosphere and irradiated with ultraviolet light generated from a Hanovia low pressure (16W) lamp. After 48hrs the reaction was stopped and the solvent removed to yield a gum which after chromatography on silica (diethylether - 60-80° petrol) afforded the title compounds. The α-isomer has R_f 0.687, m.p. 104-105°C. Yield 0.18g (25%); ν_{max}(Nujol) 1750, 1360, 745cm^{-1}; δ_H($CDCl_3$), 7.20(8H,m), 7.0(1H,m), 3.85,3.65(2x1H,dq,J_1=8Hz, J_2=3Hz, OCH_2CH_3), 2.90(2H,m H_2-4), 2.42(1H,m,H-2), 2.26(1H,dt,J=12Hz, J_2=3Hz, H-2), 2.00(2H,m,H_2-3), 1.88(3H,t,J=8Hz,OCH_2CH_3) [Found: C,77.8; H,6.9; N,4.65 $C_{20}H_{21}NO_2$ requires: C,78.1; H,6.9; N,4.6%]

The β-isomer has R_f 0.5, m.p. 115-116°C; ν_{max}(Nujol) 1770, 1510, 1390, 780, 760cm^{-1}; δ_H($CDCl_3$) 7.37(1H,dd,J_1=9Hz, J_2=1.5Hz), 7.3-7.15(7H,m), 7.05(1H,m), 3.32 and 3.00(2x1H,dq,J_1=14Hz, J_2=8Hz, OCH_2CH_3), 2.93(2H,m,H_2-4), 2.56(1H,dt,J_1=14Hz, J_2=3Hz, H-2), 2.11(1H,m,H-2), 1.92(2H,m,H_2-3), 1.89(3H,t,J=8Hz, OCH_2CH_3) [Found: C,77.8; H,6.9; N,4.65, $C_{20}H_{21}NO_2$ requires: C,78.1; H,6.9; N,4.6%].

Alternative preparation of spiro-[1,2, 3,4-tetrahydronaphthalene-1,4'-(3'β-ethoxy-1'-phenylazacyclobutan-2'-one)] (90)

(a) 3,4-Dihydro-1(2H)-N-phenylnaphthylimine (0.5g, 2.2mM) was dissolved in dichlorobenzene (30cm^3). To this, ethyl diazoacetate (0.25g, 2.2mM) was added. The mixture was heated to 100°C for $^1/_2$hr (tlc analysis indicated no reaction) and then to 140°C for 15 mins, and finally to 150°C for $^3/_4$hrs. Tlc analysis then showed a new spot with an R_f similar to that of the isomer of spiro-[1,2,3,4,-tetrahydronaphthalene-1,4'-(3'β-ethoxy-1'-phenylaza-cyclobutan-2'-one)]. The crude mixture was chromatographed on a silica column using diethyl ether/60-80°C petroleum ether (1:5) as eluant to give the β-isomer(136) (0.1g, 15%). The infra red spectrum of this compound showed a band corresponding to a β-lactam carbonyl stretching frequency at ν_{max} 1770cm^{-1} and the melting point the same as in previous experiments. The identity of this compound was confirmed by a mixed m.p.

(b) The above reaction was repeated in the presence of a catalytic amount of rhodium acetate. The mixture was heated to 130°C for 6hrs but no change to the starting material was observed.

Effect of heat and aqueous alkali on spiro[1,2,3,4-tetrahydro-naphthalene-1, 4'-(3'β-ethoxy-1'-phenylazacyclobutan-2'-one)](90)

1,2,3,4-Tetrahydronaphthalene-1,4'-(3'β-ethoxy-1'-phenylazacyclobutan-2'-one)] (0.1g, 0.3mM) was dissolved in toluene (50cm^3) and placed in a flask connected to a reflux condensor. The mixture was heated via an oil bath and tlc analytical checks were made at every 5°C rise in the oil bath temperature. No change to the starting material was observed at temperatures up to 110°C and the compound was stable at this temperature even after 2 hrs. Similarly the compound survived treatment with aqueous sodium hydroxide solution at room-temperature.

13-Phenyl[a,i]dibenzo-5,6,7,8-tetrahydrocabazole(119)

N-Butyllithium (17mMol) in dry tetrahydrofuran (10cm^3) was added slowly (15 mins) to a suspension of trimethylsulphonium iodide (3.46g,17mM) in the same solvent (20cm^3) maintained at 0°C and protected by a nitrogen atmosphere. The imine (88) (2.5g,11mM) in tetrahydrofuran (10cm^3) was then introduced and the reaction mixture stirred overnight. At the end of this time air was admitted and within a short period a new spot appeared on tlc plates used to monitor the reaction. The intensity of this new spot gradually increased during the course of 48hrs. Water was then added and then dichloromethane, the organic phase was removed and evaporated to afford an oil which was chromatographed on silica. Elution with 20% diethyl ether in 60-80°C petrol gave firstly unreacted imine (60%) and then the title compound (0.58g, 15%) as colourless prisms m.p. 197-198°C; $\lambda_{max}(\epsilon)$ 348(113,600), 364(114,232); ν_{max} 1600, 1490, 780, 710cm^{-1}; $\delta_H(CDCl_3)$ 7.5(5H,m,$C_6\underline{H}_5$-), 7.18(2H,dd,$\underline{J}$=8Hz, $\underline{J}_2$=1Hz, H-1,H-2),

6.91(2x2H, 2xm, H-3, H-4, H-10, H-11), 6.25(2H,dd,J_1=8Hz, J_2=1Hz, H-4, H-9), 2.92(2x2H, 2xt, J=7Hz, H_2-6, H_2-7), 2.69(2x2H, 2xt, J=7Hz, H_2-5, H_2-8)

$\delta_C(CDCl_3)$, 140.3(s), 136.6(s), 131.5(s), 130.3(s), 129.7(s), 129.0(d), 128.5(d), 128.2(d), 126.0(d), 124.6(d), 120.5(s), 30.8(t), 20.6(t).

Subsequently the yield of this product was increased to 40% by reacting the substrate (88) with one mol. equivalent of n-butyllithium at 0°C under an atmosphere of nitrogen and then allowing the reaction mixture to warm to room-temperature exposed to atmospheric oxygen. After a further 24hrs the solvent (THF) was removed and the product purified by chromatography (as before).

1-Methylamino-1,2,3,4-tetrahydronaphthalene-1-ol(145)[80]

α-Tetralone (4.5g, 0.03M) and trimethylsilylcyanide (5cm^3) containing a trace of anhydrous zinc iodide were sealed in a flask and stored at 0°C for several days (the whole operation was conducted so that exposure to atmospheric moisture was avoided). At the end of this time the reaction mixture was syringed into a suspension of lithium aluminium hydride (1.5g,0.04M) in dry tetrahydrofuran (THF) (100cm^3) maintained at 0°C. The cooling bath was then removed and the contents of the flask heated at reflux for 3hr. Water (5cm^3) and then 30% sodium hydroxide (2cm^3) were introduced into the cooled medium and then more water (5cm^3). The tetrafuran layer was separated and the aqueous layer was extracted with diethyl ether (3x20cm^3). Finally the organic phases were combined, dried and evaporated to yield the title compound as a

colourless oil (4.9g, 90%). ν_{max} 3380, 3330, 2940, 1490, 1450, 760, 750cm^{-1}; δ_H $CDCl_3$ 7-7.5(m,4H, aromatics), 2.8(m,4H,$C\underline{H}_2$-NH_2, C_4-H_2), 2.2(bs,3H, exchanged with D_2O, $N\underline{H}_2$, $O\underline{H}$), 1.95-1.6(m,4H, C_2-H_2, C_3-H_2); m/z 177.

1-[N-(Triphenylmethyl)methylamino]-1,2,3,4-tetrahydronaphthalene-1-ol(147*)

Triphenylmethylchloride (1.1g, 0.04M) in Analar chloroform (10cm^3) was added to a solution of 1-methylamino-1,2,3,4-tetrahydronaphthalene-1-ol (0.7g, 0.04M) in Analar chloroform (40cm^3) and anhydrous triethylamine (2cm^3) maintained at 0-5°C. After the addition the reaction mixture was allowed to warm to room temperature during 24hrs. The solvent was then evaporated off and the residue chromatographed on neutral grade alumina eluting with ethylacetate/60-80°C petroleum ether (1:5) to give the title compound as a colourless crystalline solid, m.p. 158-159°C (0.63g, 95%). ν_{max}($CHCl_3$) 3450, 3060, 1490, 1450cm^{-1}; δ_H($CDCl_3$), 7.6-7.0(m,19H, aromatics), 2.9(m,1H, exchanged with D_2O), 2.8-2.2(m,5H), 2.0-1.85(m,4H) [Found: C, 85.5; H, 7.1; N, 3.1, $C_{30}H_{29}NO$ requires: C, 85.9; H, 6.9; N 3.3%].

1-[(N-Triphenylmethyl)methylamino]-3,4-dihydronaphthalene(153)

A mixture of 1-[(N-triphenylmethyl)methylamino]-1,2,3,4-tetrahydronaphthalene-1-ol (1g, 0.024M), triphenylphosphine (0.73g, 0.027M), carbon tetrachloride (0.4m^3), dry triethylamine (0.21g, 0.024M), and dry acetonitrile (50cm^3) was heated at 50°C for 24hrs. The solvents were then removed in vacuo and the residue chromatographed on a column of silica using diethyl ether - 60-80°C petroleum ether (1:1) as the eluant. This

* other related experiments are found in the supplement on p.174.

gave the title compound as a colourless crystalline solid (0.38g, 40%), m.p. 104-106°C; $\lambda_{max}(\epsilon)$ 220(22,200)nm; $\nu_{max}(CHCl_3)$ 1600, 1490, 1450cm^{-1}; $\delta_H(CDCl_3)$, 7.0-7.6(19H,m, aromatics), 6.24(1H,t,J=5Hz, C_2-H), 3.08(2H,d,N-CH_2). When the ^{1}H n.m.r. sample was shaked with D_2O this signal collapsed to a singlet and that at δ1.67 disappeared. 2.68(2H,m,C_4-H_2), 2.30(2H,m, C_3-H_2), 1.67(1H,t,NH). Elemental analyses results were variable. m/z M^+ 401.2174; $C_{30}H_{27}N$ requires: 401.2205.

1,2,3,4-Tetrahydronaphthyl-1,5-spiro-1',3'-oxazolidin-2'-one(158)

1-Aminomethyl-1,2,3,4-tetrahydronaphthalene-1-ol (2g, 0.011M) was added to a suspension of anhydrous potassium carbonate (1.6g,0.011M) in dichloromethane (50cm^3) maintained at -60°C. To this was added phosgene (14cm^3 of a 12% solution in toluene) and the mixture was allowed to warm to room temperature during 1^1/$_2$ days. The solvent was then removed in vacuo and the residue chromatographed on alumina (neutral grade) using ethyl acetate/ 60-80°C petroleum ether (1:1) as eluant to afford the title compound as a colourless solid(0.7g, 30%), m.p. 149-150°C, $\lambda_{max}(\epsilon)$ 213(7,660)nm; ν_{max}3300, 1750, 1490, 1430 and 760cm^{-1}; $\delta_H(CDCl_3)$ 7.5-7.0(m,4H, aromatics), 6.7(s,1H,NH), 3.7(2xd,2H, J=9Hz, CH_2-N), 2.9(t,2H, J=5.8Hz, C_4-H_2), 2.5-1.8(m,4H, C_2-H_2,C_3-H_2); $\delta_C(CDCl_3)$, 137.3(2xs, C-4a, C-8a), 129.0, 128.6, 126.9, 126.6(4xd), C-5, C-6, C-7, C-8), 82.2(s,C-1), 54.3(t,C-4'), 35.8(t,C-4), 29.1(t,C-2), 19.7(t,C-3); m/z M^+203.0964 $C_{12}H_{13}NO_2$ requires: 203.0946

Alternative preparation of 1,2,3,4-tetrahydronaphthyl-1,5'-spiro-1',3'-oxazolidin-2'-one(158)

The aminoalcohol (145) (3.0g, 0.017M) in dry tetrahydrofuran (20cm^3) was added slowly to a solution of N,N'-carbonyldiimidazole (2.7g, 0.017M) in the same solvent (50cm^3). The reaction mixture was stirred for a day and the solvent then evaporated off and the residue triturated several times with carbon tetrachloride. It was then dissolved in a small volume of ethyl acetate and chromatographed on neutral grade alumina eluting with ethylacetate/60-80°C petroleum ether (1:1) to yield the title compound which had identical physical characteristics to those described above. The yield was 1.1g, 36.6%.

1-[N-methoxycarbonyl)methylamino-1,2,3,4-tetrahydronaphthalene-1-ol(159)

Methyl chloroformate (1.6cm^3) was added in small portions to a solution of 1-methylamino-1,2,3,4-tetrahydronaphthalene-1-ol (2.4g, 0.014M) in dry pyridine (30cm^3) (previously distilled from potassium hydroxide). The reaction mixture was stirred for 12 hrs and water (15cm^3) and diethyl ether (100cm^3) were then added. The ether layer was collected and the aqueous phase was extracted several times with portions of diethyl ether. The ether layer and extracts were combined, washed with water, dried and evaporated to afford the title compound as a colourless solid mpt 97°C(2.1g, 70%). ν_{max} 3420, 3340, 2940, 1700, 1540, 1250 and 760cm^{-1}; δ_H($CDCl_3$), 7.45-7.05(m,4H, aromatics), 4.25(s,3H,$C\underline{H}_2$-$N\underline{H}$), 3.95(s,3H,$OC\underline{H}_3$), 2.85(t,2H, $\underline{J}$=2.5Hz, C_4-$\underline{H}_2$), 2.3-1.8(m,5H,C_2-$\underline{H}_2$, C_1-$O\underline{H}$); δ_C($CDCl_3$) 151.5(s,$\underline{C}O_2CH_3$), 137.6, 135.7(2xs, C-4a, C-8a), 129.2, 128.9, 127.0, 126.1,

(4xd, C-5, C-6, C-7, C-8), 78.7(s,C-1), 56.6(q,$CO_2\underline{C}H_3$), 54.0(t,$\underline{C}H_2NH$), 35.5(t,C-4), 28.8(t,C-2), 19.5(t,C-3), [Found: C, 66.2; H, 7.5; N,6.- $C_{13}H_{17}NO_3$ requires: C,66.4; H,7.2; N,6.0%].

1-(N-Methylmethylamino)-1,2,3,4-tetrahydronaphthalene-1-ol(160)

A suspension of lithium aluminium hydride (0.87g, 0.22M) in dry tetrahydrofuran (30cm^3) was maintained at 0°C in a vessel protected from atmospheric moisture. To this was added 1-[N-(methoxycarbonyl)methylamino]-1,2,3,4-tetrahhydronaphthalene-1-ol (0.9g, 0.028M) in tetrahydrofuran (20cm^3). After the initial reaction had subsided, the temperature inside the flask was allowed to rise to room conditions during a period of 20hrs. Aqueous sodium hydroxide (20%) was added carefully drop by drop to the reaction mixture until all the excess reagent had been destroyed. The mixture was then diluted with more tetrahydrofuran (50cm^3) and filtered. Finally, the filtrate was collected and the solvent removed to give the title compound as a yellow oil (0.73g, 98%), ν_{max} 3400, 3320, 2940, 1450, 760 and 730cm^{-1}; $\delta(CDCl_3)$, 6.9-7.4(m,4H,aromatics), 2.8(bs, 2H, N-$\underline{C}H_2$), 2.50(s,3H,$\underline{C}H_3N$), 2.3(bs,1H,$\underline{N}H$), 1.7-2.2(m,7H,3x$\underline{C}H_2$ + OH); m/z 191. Attempts to obtain a satisfactory elemental analysis failed.

1,2,3,4-Tetrahydronaphthyl-1,5'-spiro-3'-methyl-1',3'-oxazolidin-2'-one(161

A mixture of anydrous potasium carbonate (10.4g, 0.076M), dry dichloromethane (50cm^3) and 1-[N-methyl)aminomethyl]-1,2,3,4-tetrahydronaphthalene-1-ol (0.73g, 0.038M) was maintained at -60°C and treated with phosgene (4.7cm^3 of a 12% solution in toluene). After two hours, the reaction

mixture was allowed to warm gradually to room temperature during 24 hrs. The solvents were then removed in vacuo and the residue chromatographed on neutral grade alumina eluting with ethylacetate/60-80°C petroleum ether (1:1) to give the title compound as a colourless oil. ν_{max} 3450, 2940, 1750, 765cm^{-1}; $\delta_H(CDCl_3)$ 7.4-7.05(m,4H, aromatics), 3.62(2xd, 2H, J=8.5Hz, C_4-H_2), 2.98(s,3H,N-CH_3), 2.8(m,2H,C_4-H_2), 2.3-1.95(m,4H,C_2-H_2-C_3-H_2); $\delta_C(CDCl_3)$, 183.3(s,C-2^1), 137.2(2xs, C-4a, C-8a), 128.9, 128.4, 126.8, 126.3(4xd, C-5, C-6, C-7, C-8), 78.1(s,C-1), 60.6(t,C-4^1), 35.9(t,C-4), 31.0(q,NCH_3), 29.0(t,C-2), 19.6(t,C-3); m/z M^+ 217.1103 $C_{13}H_{15}NO_2$ requires: 217.1096.

Attempted thermolysis of 1,2,3,4-tetrahydronaphthyl-1,5'-spiro-3'-methyl-1',3'-oxazolidin-2'-one

The oxazolidinone(161) (0.9g, 4.1mM) was dissolved in anhydrous toluene (50cm^3) and heated at reflux for 24 hrs. No sign of reaction was shown on tlc analysis.

Photochemical reaction of 1,2,3,4-tetrahydronaphthyl-1,5'-spiro-1',3'-oxazolidin-2-one(158)

The oxazolidinone(158) (0.61g, 3.00mM) was placed in a photochemical reactor (500cm^3) and anhydrous methanol (400cm^3) was added. This solution was irradiated with a low pressure Hanovia lamp (16W) for a day. Tlc analysis of the product showed no change had occurred and the oxazolidinone was recovered after the reaction.

1,2,3,4-Tetrahydronaphthyl-1,2'-spiro-oxirane(154)

Dimethylsulphoxonium iodide (30g, 0.14M) was added rapidly to a well stirred suspension of sodium hydride (3.3g, 0.14M) in anhydrous dimethylsulphoxide ($50cm^3$) protected by an atmosphere of nitrogen and maintained at 0°C. After the addition, stirring was continued for a further 15 mins and 1-tetralone (10g, 0.07M) was then introduced. The reaction mixture was allowed to warm to room temperature and it was then heated to reflux for 1h and finally set aside to cool overnight.

The next day water ($100cm^3$) was added and the product extracted into diethyl ether ($2x100cm^3$). Evaporation of the combined, dried extracts afforded the oxirane, a known compound, as an oil (11g, 98%); ν_{max} 3140, 2940, 1490, 1450, $760cm^{-1}$; $\delta_H(CDCl_3)$ 7.55-6.85(4H,m, aromatics), 2.90(2H,s, $C\underline{H}_2O$), 2.89-1.59(6H,m, $C_2-\underline{H}_2$,$C_3-\underline{H}_2$,$C_4\underline{H}_2$); m/z 160 [Found: C, 82.3; H, 7.1 calculated for $C_{11}H_{12}O$, C, 82.5; H, 7.5 %].

1-Hydroxymethyl-3,4-dihydronaphthalene(156)[95]

The epoxide (154) (1.5g, 0.009M) in dimethylformamide ($40cm^3$) containing benzylamine (1g, 0.009M) was saturated with hydrogen chloride during 3hrs. Water was then added and sufficient sodium carbonate to render the mixture neutral to litmus. This was then extracted with diethyle ether ($3x20cm^3$) and the combined extracts, dried and evaporated to yield a gum. Chromatography on neutral grade alumina using diethyl ether and 60-80°C petroleum

ether (1:1) gave the alcohol (207) (0.4g, 30%) as an oil. Early fractions containing unreacted starting material (0.9g, 60%); ν_{max} 3400, 2940, 1480, 1450, 750, 730cm^{-1}; $\delta_H(CDCl_3)$ 7.3-7.0(4H,m,aromatics), 6.0(1H,t, J= 4Hz, C_2-H), 4.5(2H,s,CH_2OH), 3.0-2.7(2H,m, C_4-H_2), 2.5-2.2(2H,m,C_3H_2), 1.9(1H,bs, exchanged with D_2O, -OH); m/z M^+ 160.0888; $C_{11}H_{12}O$ requires: 160.0867.

Alternative preparation of 1-hydroxymethyl-3,4-dihydronaphthalene(156)

The epoxide (154) (0.8g, 0.0005M) in dry tetrahydrofuran (50cm^3) containing zinc iodide (1.75g) was stirred for 15 mins and benzylamine (0.5g, 0.005M) was then added. The reaction mixture was allowed to stand for 12hrs, the solvent, was then removed and the residue chromatographed on neutral grade alumina using diethyl ether/60-80°C petroleum ether (1 :1) as eluant. This gave the alcohol (207) as a colourless oil (0.3g, 50%), all spectroscopic data matched those of the compound previously prepared.

3,4-Dihydro-1(2H)-methylenenaphthalene(182)[94]

n-Butyllithium in dry diethylether (95cm^3, 0.14M solution) was added slowly to a mixture of triphenylphosphonium iodide (58.6g, 0.14M) in dry diethyl ether (250cm^3). After 20 mins., tetralone (12cm^3, 0.9M) was introduced into the reaction mixture which was stirred at room temperature for a day and then heated at reflux for 1 hr.

Water was then added to dissolve the salts which had formed and the organic layer was dried and evaporated to give an oil. This material was chromatographed on alumina using 60-80°C petrol to elute the title compound (6.5g, 50%) as a colourless oil; ν_{max} 1640cm^{-1} $\delta_H(CDCl_3)$, 7.2-7.0(4H,m, aromatics), 5.5 and 4.9(2x1H, 2xd J=0.7Hz, $=CH_2$), 2.8(2H,t,J=4Hz, C_4-H_2, 2.6(2H,bt, J=4.5Hz, C_2H_2), 1.9(2H,t, J_1=4.5Hz, J_2-4Hz, C_3-H_2); $\delta_C(CDCl_3)$, 143.5, 137.3(2xs, C-4a, C-8a), 129.2, 127.6, 125.9, 124.2(4xd, C-5, C-6, C-7, C-8), 107.8(t, exocyclic carbon), 33.3(C-4), 30.5(C-2), 23.8(C-3), the resonance position of C-1 was not detected with certainty. m/z 144

1-Azido-1-iodomethyl-1,2,3,4-tetrahydronaphthalene(185)

Sodium azide (2.3g, 0.035M) and anhydrous acetonitrile (40cm^3) were cooled to -15°C and treated with iodine monochloride (2.6g, 0.02M) in anhydrous acetonitrile (4cm^3). The addition took place over a period of 15 mins. and the reaction mixture was stirred for a further 10 mins. before 3,4-dihydro-1(2H)-methylenenaphthalene (2g, 0.014M) was introduced. The reaction mixture was then allowed to stir and warm to room temperature overnight.

Water (30cm^3) was then added and the product extracted into diethyl dether (2x20cm^3). The combined extracts were washed with 5% sodium thiosulphate, followed by water, dried and evaporated to afford a yellow oil (4.2g, 95%);

ν_{max} 2960, 2120, 1500, 1450, 1260, 770, 740cm^{-1}; δ_H($CDCl_3$) 7.5-7.0(4H,m, aromatics), 3.45(2H,s, $\underline{CH_2}I$), 2.78(2H,t, $\underline{J}$=4Hz, C_4-H_2), 2.4-1.6(4H,m, C_2-H_2), C_3-H_2); δ_C($CDCl_3$), 137.4, 134.5(2xs, C-4a, C-8a), 129.6, 128.5, 126.7(3xd, C-5, C-6, C-7, C-8), 63.8(s,C-1), 34.4(t,C-4), 29.4(t,C-3), 19.5(t,C-2), 16.6(t,$\underline{CH_2}I$); $\underline{m/z}$ 313.

1,2,3,4-Tetrahydronaphthyl-1,2'-spiroaziridine(173)

1-Azido-1-iodomethyl-1,2,3,4-tetrahydronaphthalene (1.6g, 0.01M), in dry diethyl ether (15cm^3) was added slowly to a suspension of lithium aluminium hydride (1.2g,0.03M) in the same solvent (10cm^3) maintained at 0°C. After the addition the reaction mixture was allowed to warm to room temperature overnight. Excess reagent was then destroyed by the addition of 20% aqueous sodium potassium tartarate solution and the ether layer decanted off. The residue was washed twice with diethyl ether (100cm^3) and the combined organic phases were then dried and evaporated to yield the aziridine (173) as a very unstable colourless oil (0.1g ,60%); ν_{max} 3300, 2940, 1500, 1460, 760cm^{-1}; δ_H($CDCl_3$)7.25-6.80(4H,m, aromatics), 2.90(2H,bt,$\underline{J}$=4Hz, C_4-$\underline{H_2}$), 2.12(1H,s,$\underline{NH}$, exchanged with D_2O), 2.05-1.78(6H,m $\underline{CH_2}N$, C_2-H_2, C_3H_2); $\underline{m/z}$ 159.

Thermolysis of 1,2,3,4-tetrahydronaphthyl-1,2'-spiroaziridine(173)

The spiro aziridine (173) (0.1g, 0.6mM) was dissolved in dry ether (20cm^3) and added to a flask (50cm^3) containing sand (2g). The ether was removed under reduced pressure. This material was then heated in a hot oil bath 9190°C) for $^1/_2$ hr. A little sample was then removed and the analysis indicated the formation of a less polar spot. Heating was continued for another $^1/_2$ hr and

by that time most of the aziridine had been used up. The reaction mixture was cooled and diethyl ether was added and the sand filtered off. Tlc analysis of the filtrate now showed a very complex mixture.

1-[N-Methyl] methyl carbamate-3,4-dihydronaphthalene(186)

The pure aziridine (173) (0.01g,0.06mM) was added to dry triethylamine ($10cm^3$) in a sealed flask under an inert atmosphere at 0°C. One equivalent of methylchloroformate was syringed into the above flask slowly. The mixture was stirred at 0°C for $1\frac{1}{2}$ hrs and the resultant product was chromatographed on alumina column with ether/60-80° petroleum ether. This gave the title compound (186) in 40% yield as an oil; ν_{max} 1700, 1440, $760cm^{-1}$; δ($CDCl_3$, 400 MHz), 7.00-7.25 (m,4H,aromatics), 6.03 (t,1H,J=4Hz,C_2-H), 4.72 (bs,1H,[exchangeable (D_2O shake)],-NHO, 4.2 (bd,2H,J=5Hz,-CH_2-NH-), 3.6 (S,3H,-OCH_3), 2.75 (t,2H,J=8Hz), C_4-H_2), 2.2 (m, 2H,C_3-H_2); m/z 217.1119 $C_{13}H_{15}NO_2$ requires: m/z 217.1103.

Benzyl bromide reaction with (173)

The aziridine was made by following the procedure on p 165. The lithium aluminium hydride was allowed to settle to the bottom of the flask. The clear ethereal layer containing the aziridine (0.2g,1.25M) was transferred to another dry sealed flask. Benzylbromide (0.2g,1.25M) was added at 0°C. The ir and nmr of the purified product showed no desirable products.

(a) Reaction of ethyldiazoacetate with (173)

Using the aziridine (173) (0.2g,1.25M) described in p 165, ethyl diazoacetate (0.14g,1.25M) was added in the presence of trace rhodium II acetate. TLC monitoring was carried out at regular intervals for $2^1/_2$ hrs. Meanwhile, the temperature was increased gradually from 40° to 80°. The aziridine disappeared but only breakdown products were given.

(b) Reaction of trityl chloride with (173)

The same procedure was repeated here using trityl chloride (see p 157). TLC observation showed the disappearance of the aziridine but no significant product was obtained.

Preparation of bis(benzonitrile) palladium dichlordie[101]

Anhydrous palladium II chloride was suspended in benzonitrile ($50cm^3$) and the mixture was warmed to 100°. Twenty minutes later the red solution was filtered hot and the filtrate poured into 40-60° petroleum ether ($300cm^3$) and the bright yellow solid was removed by filtration.

Reaction of the palladium complex with 3,4-dihydro-1(2H)methyl-enenapthalene(182)

The palladium complex (0.026g,0.07mM) was reacted with 3,4-dihyro-1(2H)-methylenenapthalene (0.1g,0.7mM) in dry THF (10cm^3) for 30 minutes. To this benzylamine was added (0.669g,6.3mM) at -78^o (acetone/CO_2).

The mixture was left stirring for a day while the temperature was reaching room temperature gradually. During this first 30 minutes and before addition of the amine, tlc showed the appearance of a new spot. However, when the final reaction mixture was columned the majority of the starting material was returned and no other significant compound.

Tosyl azide reaction with 3,4-dihydro-1(2H)-methylenenapthalene

Tosyl azide (1.85g,9.4mM) [prepared by the reaction of sodium azide with tosyl chloride] was added to a dry photochemical vessel containing a dry, oxygen free cyclohexane (400 cm^3). To the above mixture the 3,4-dihydro-1C2H)-methylenenapthalene (182) (0.9g,6.3mM) was added. Irradiation was performed with ultraviolet light generated from a Hanovia medium pressure (240w) lamp. Two hours later the starting methylene compound disappeared as was shown by tlc and the crude was columned chromatographed on neutral aluminia using ether/60-80 petroleum ether to afford a white solid (50%) ν_{max} 3250, 1580, 1300 and 800 cm^{-1}; δ($CDCl_3$,270MHz), 7.8 (2d,4H,aromatics), 3.2 (m,1H, [exchangeable with D_2O], 2.6 (S,3H,-$\underline{CH_3}$), 1.9-1.2(m,10H, cyclohexane ring); $\underline{m/z}$ 234.

Similar results were produced when cyclohexane was replaced with benzene, chlorobenzene and nitrobenzene.

3-(2-Furanyl)-indole (214)

(E,2-2-(2-Nitro-1-phenylethen-1-yl) furan (212) (4g,0.0186M), a known compound [109], was placed in a 100 cm^3 r.b.f. connected to a condenser under a nitrogen atmosphere. Into was syringed 20 cm^3 of triethylphosphite. The mixture was heated to 166°C for 6-8 hours. The analysis showed the presence of a more polar component which illuminated brightly under UV irradiation. At the end of reaction time excess triethylphosphite was evaporated off under reduced pressure. The crude was columned chromatographed on fine flash silica, using 10% ethylacetate in 60-80° petroleum ether increasing the polarity gradually, to give the title compound as a yellow solid which turned into a browny green solid very soon afterwards (1.7g, 50%); mpt. 90°; $\nu_{max}(CHCl_3)$ 3466 cm^{-1}, 1605 cm^{-1}; $\delta(CHCl_3,60$ MHz) 6.5(m,2H,furanyl protons), 7.2(m,3H,aromatics), 7.4(m,2H, one aromatic and one furanyl proton), 7.9(bm,2H,-NH [exchanged with D_2O],NH-CH),m/z 183.

Reaction of 3-[2-furanyl]-indole with hydrochloric acid

3-[2-furanyl]-indole (0.5g,2.7mM) was added to a mixture of 2MHCl in ether. This was stirred at room temperature for 2 1/2 hours and then refluxed gently for 2 hours. No change to the starting material has occurred.

Then this indole was added to a mixture of 5MHCl and THF, refluxed for an hour. TLC analysis showed a baseline spot, and will not separate with most polar solvents like methanol. Complete breakdown of the starting material has

probably occurred. This reaction was therefore repeated using less concentrated hydrochloric acid stirring at room temperature. In this case not much change occurred.

1-(Indol-3'-yl)-4-(indol-3-yl furan-2'-yl)-4-hydroxy-butanone (217)

Compound (215) (0.8g,4.4mM) was added to a mixture of 75% acetic acid and a drop of concentrated sulphuric acid which was allowed to stir at room temperature for two hours. This showed no starting material was present. This mixture was diluted with ethylacetate and water, washed with sodium hydrogen carbonate, separation of organic layer and drying over magnesium sulphate. The brown gum produced after solvent evaporation was columned chromatographed on silica ten times, in order to obtain the pure form of the title compound (217) as a white solid. $\nu_{max}(CHCl_3)$, 3460 cm^{-1} due to -NH group absorption, 1650 cm^{-1} due to the carbonyl group adjacent to the indole system; δ_H(270MHz, DMSO) 11.93(S,1H,-NH of the furanyl indole), 11.29 (S,1H,-NH of the ketonic indole), both these signals disappeared on D_2O shaking, 8.39(d,1H,J-2.93Hz,-CH-NH), 7.57(d,1H, J = 2.56Hz,-CHNH), 7.0-8.3 (m,8H, aromatics), 6.4(d,1H, J = 3.3Hz, furanyl proton-4), 6.2(d,1H,J = 2.9Hz, furanyl proton-3), 4.9(S,1H, [exchanged with D_2O],-OH), 3.3-3.8 (m,5H, aliphatics),δ_C (270MHz, DMSO) 194.189 (carbonyl group), 153.272 (CH-NH), 148.877 (CH-NH), 136.2374-103.128 (18 carbon-13 resonances of the two indole units and one furan unit), 37.884 (-C-H), 39.441 ($-CH_2$ adjacent to the carbon atom carrying the hydroxyl group), 63.346 ($-CH_2$ adjacent to the carbonyl group); m/z 366 (corresponds to the molecular ion after the loss of a water molecule), [found : 366.1348 $C_{24}H_{20}N_2O_2$ requires 366.1366].

Reaction of (214) with maleic anhydride

Compound (214) (0.2g,1.1mM) was added to a solution of maleic anhydride (0.12g,1.2mM) in dry ether. The mixture was left stirring at room temperature for 3 hours, but TLC analysis showed no change at all. This mixture was refluxed gently for another 4 hours and again starting material stayed.

Reaction of (214) with hydrazine sulphate[115]

(0.4g,2.19mM) of (214) was added to a solution of hydrazine sulphate (0.28g,2.19mM) with 2 cm^3 of 10% sodium hydroxide in THF/methanol mixture. This was left stirring at room temperature overnight and no reaction was shown by TLC analysis. Then it was refluxed for 3 hours which again led to no reaction.

Reaction of (214) with Cookson Reagent*

The indole (214) (0.05g,0.27mM) was dissolved in 5 cm^3 THF in a 25 cm^3 r.b.f. placed in an ice bath under nitrogen atmosphere. To this Cookson reagent (0.05g,0.27mM) in THF was added dropwise over 10 minutes using a syringe. TLC showed a base line spot and no starting material in about 1/2 hour reaction time. It was not possible to separate the tarry substance obtained.

Reaction of (214) with bromine

Compound (214) (0.1g, 8.054mM) was dissolved in 1,4-dioxane. To this mixture (at 0°C) was added bromine (0.09g, 1.1mM). TLC showed no starting material was left after 20 minutes and a complex mixture of many closely separated components occurred.

*Cookson reagent is 4-phenyl-1,2,4-triazoline-3,5-dione which was used as a dienophile for the furan in (214).

Dilution effect on the reaction of (214) with acetic acid

In a 250 cm^3 flask was placed 75% of acetic acid (50 cm^3) and a drop of concentrated sulphuric acid. To this was added a diluted solution of (214) (0.2g in 150 cm^3 of ether) dropwise. This was left stirring at room temperature for 6 hours. TLC analysis showed the slow appearance of a spot similar to the polar compound (217). This was then confirmed by ir spectrometry.

2-Bromo-1-(1-hydroxy-2-nitroethan-yl)benzene (218)

In a 2-necked 100 cm^3 r.b.f. connected to a dropping funnel and a thermometer, was placed 2-bromobenzaldehyde (5g, 0.027M) and nitromethane (1.6g, 0.027M) stirring in an ice bath. The dropping funnel contained sodium hydroxide solution (1.1g/1 cm^3) which was added dropwise so that the temperature was allowed to stay constant around 15°C. The mixture was stirred to 1 1/2 hours. TLC monitoring showed no starting material. The mixture was diluted with water and then added slowly to hydrochloric acid solution (1 : 2/HCl:H_2O). The yellow oil was extracted with ether , dried and concentrated to give the title compound (5.9g, 90%); ν_{max} 3500,1550 cm^{-1}; $\delta(CCl_4, 60MHz)$7.2-7.7(m,4.H, aromatics), 5.8(m,1H,-COH-H), 4.65(d,2H,J = $5H_3$,-CH_2NO_2), 3.2(d,1H,J = $5H_2$,-OH [exchanged with D_2O on shaking]); m/z 228 (equivalent to the molecular ion less water, i.e. 246-18 = 228) $C_8H_8BrNO_2$.

2-Bromo nitro styrene (219)

Using a reflux apparatus, the compound (218) (0.9g, 3.6mM) was placed with acetic anhydride (0.09 cm^3, 1.8mM). Two drops of pyridine was added. The reaction mixture was heated to 100°C for two hours and until no starting material left. Excess acetic anhydride was removed under reduced pressure and the crude product was columned chromatographed on silica using ether/60-80° petroleum ether starting with 5% mixture. The pure pale yellow solid of the title compound was then analysed, mpt/ 80-81°C; ν_{max} 1620 cm^{-1}; δ_H($CDCl_3$, 60MHz) 7.2-7.85(m,4H,aromatics + the 2H of the vinyl protons); m/z 227 + 229 [found: 228.9562 $C_8H_6BrNO_2$ requires 228.9561].

2-(2-Nitro-1-[2-bromophenylethan]-1-yl) furan (220)

2-bromonitrostyrene (6.0g, 0.026M) was placed in a 100 cm^3 r.b.f. containing furan 25 cm^3 and zinc iodide (2.09g, 6.6mM) under nitrogen atmosphere. This was stirred at RT for a week and then refluxed for a day. TLC showed that most starting material was used up. Excess furan ws removed under reduced pressure and the crude was columned chromatographed on silica using ether/60-80° petroleum ether to give a yellow oil (4.6g, 67%), ν_{max} 1540 cm^{-1}; δ_H($CDCl_3$,60MHz) 7.3-7.8(m,4H,aromatics + one furanyl proton), 6.2-6.4(m,2H,furanyl protons, C-3 and C-4), 5.45(t,1H,J = 8.7Hz, -CH-CH_2), 4.7(d,1H,J = 2.0Hz,-CH-CH_aH_b), 4.85(d,1H,J = 2.0Hz, CH-CH_aH_b); m/z 269 $C_{12}H_{10}BrNO_3$].

SUPPLEMENT

Preparation of (146)

The trityl amino alcohol (147) [0.19g,0.45mM] was placed in a dry flask containing dry pyridine (10cm^3) and placed in an ice bath. Mesyl chloride (0.31g,2.72mM) was added slowly to the above flask and left stirring for 6 hrs. TLC showed a less polar spot. The crude was columned chromatographed on alumina using 10% ether 60-80° petroleum ether, to give (146) as an oil (50%) ν_{max} 3060, 2920, 1600, 1480, 1450 cm^{-1}, m/z = 497.

Reaction of (146) with sodium hydride

The mesyl compound (146) [0.03g, 0.06mM] was dissolved in dry THF under an inert atmosphere. The mixture was kept at 0°C initially and during the addition of sodium hydride (0.007g,0.3mM). After 2 hrs of reaction time the mixture was refluxed for 3 hrs and then left stirring overnight. TLC analysis was done every two hours but no reaction was shown.

Reaction of (146) with n-butyllithium

The mesyl compound (146) [0.02g, 0.04mM] was placed in a dry flask under an inert gas. n-Butylithium [0.02g, 0.04mM] was syringed in very slowly. The reaction mixture was left stirring and tlc analysis after 3 hrs showed a complex mixture and no significant product was found.

Reaction of (147) with trifluoroacetic acid

The trityl amino alcohol (147) [1g,2.4mM) was dissolved in dry THF and kept at 0°C. To this trifluoroacetic acid (0.54g, 4.8mM) was syringed into the above flask and added at a slow rate. TLC showed an immediate reaction and a baseline spot was observed. However, on basic work up, the baseline spot returned to the original position of the starting material. This was then confirmed to be the starting compound (147) via the ir and nmr spectrometry measurement.

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SPIROHETEROCYCLES DERIVED FROM TETRALONE

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Abstract: New 2-heterospirotetrahydronaphthalenes with 3-, 4- and 5-membered rings have been prepared during the development of routes to tetralone derived spiroaziridines.

Spiroaziridines of the type (1) are unknown. Their synthesis presents problems because of potential benzylic cation mediated ring opening processes. It should be noted that the corresponding spiroepoxides are, not surprisingly, very reactive.[1] We report the outcome of a number of routes to (1) in which unexpected reactions emerged, and also a successful approach to the target molecules.

Carbene 1,2-cycloaddition reactions with tetralone imine (2)[2] represented an apparently obvious initial route. However, dichlorocarbene ($CHCl_3$, NaOH, ultrasound[3]) gave, in low yield, one product, with the molecular formula $C_{19}H_{19}NO$. Spectroscopic analysis showed structure (6), although its stereochemistry cannot rigorously be assigned on the basis of available data. Presumably, reaction occurs via the enamine (3), or the N-anion, which reacts with dichlorocarbene to give imine (4). Elimination of HCl from the imine to give the alkene (5) is followed by Michael addition of ethanol (from commercial $CHCl_3$) and thence (6). An alternative pathway involving an intermediate dichlorocyclopropane can also be envisaged. Interestingly, in ethanol-free chloroform no reaction occurs under similar conditions.

A wide range of other carbenes also failed to give the target spiroaziridine, although a reaction of ethyl diazoacetate produced unexpected results. Thus, irradiation of (2) with ethyldiazoacetate (low pressure Hg lamp) gave two crystalline products in moderate yield. Carbonyl bands at 1750 cm^{-1} and n.m.r. analysis excluded the desired aziridine structure. X-Ray crystallography, however, confirmed the β-lactam structures (7) and (8),[4] arising from rearrangement of the carbene by 1,2-migration to ethoxyketene,[5] followed by 2+2 cycloaddition to the imine.

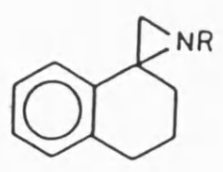
In an alternative approach to carbene cycloaddition, the reaction of dimethylsulphoxonium methylide with imine (2) was investigated. A preliminary study gave, in low yield, one isolable product of molecular formula $C_{26}H_{21}N$. A high element of symmetry was apparent from the n.m.r. spectra, and the possible structure 13-phenyl[*a*,*i*]dibenzo-5,6,7,8-tetrahydrocarbazole (9) was confirmed by X-ray crystallography.[6] This reaction necessitates an oxidation step, and if oxygen is rigorously excluded from the reaction and work-up, the compound is not formed. Conversely, if the imine is stirred with base (nBuLi or LDA) and then exposed to air, the yield was increased to 40%. A plausible reaction sequence involves addition of the imine anion to

(2), giving (10) which eliminates aniline, cyclizes and then is oxidized. Product (9) is a new dibenzocarbazole derivative in which the N-phenyl group assumes an orthogonal relationship with respect to the plane of the heterocycle.

A further synthetic approach to the target aziridines employed the vicinal aminoalcohols (11) and (12) as starting materials. Interestingly, these were not readily available from spiroepoxide (13), for example, by ring opening with benzylamine. Under standard conditions[7] the hydroxymethyldihydronaphthalene (14) was the sole product. Aminoalcohol (11) was prepared by the cyanohydrin route.[8] All attempts to cyclize (11) and (12) failed because of dehydration, giving, for example, (15). Yet another tactic involved preparing the oxazolidinone derivatives (16) and (17), followed by thermolysis. No aziridine (1) could be isolated.

The successful strategy utilized the methylidine (18) (obtained by Wittig reaction of α-tetralone) which was reacted with iodine monochloride and sodium azide in acetonitrile at -40°C, followed by immediate reduction of the unstable iodoazide (19) with lithium aluminium hydride[8] to give the aziridine (1, R=H). This unstable new compound was characterized as its N-methoxycarbonyl derivative (1, R=CO_2Me).

These explorations have thus produced new spiro 3-, 4- and 5-membered ring heterocycles, and have allowed definition of the reactivity parameters of a range of benzylically substituted tetrahydronaphthalenes. Further studies of the reactivity of aziridines (1) and synthetic applications will follow.



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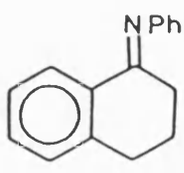

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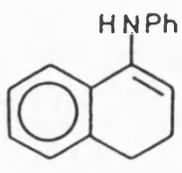

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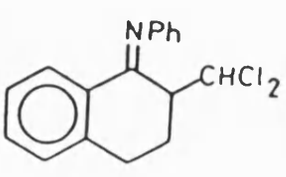

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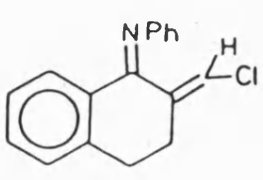

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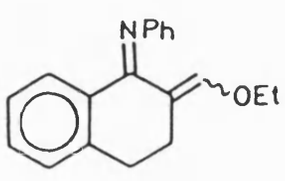

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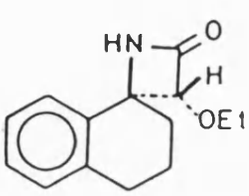

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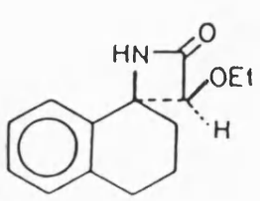

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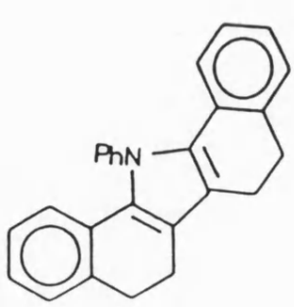

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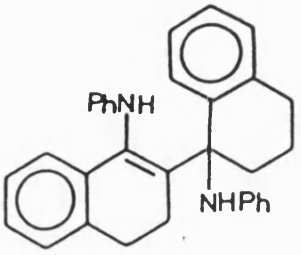

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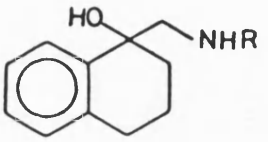
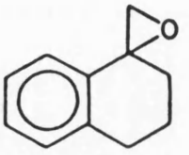


11 , R = Me
12 , R = $C(Ph)_3$



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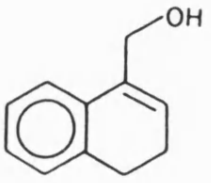

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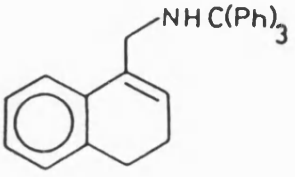

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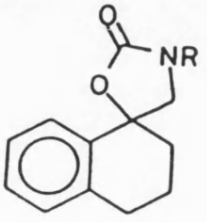
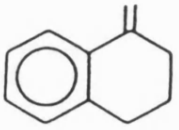


16, R=Me
17, R= $C(Ph)_3$



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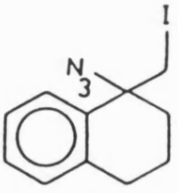

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Acknowledgements

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Experimental

U.v. spectra were recorded as solutions in 98% ethanol. ^1H n.m.r. spectra were recorded at 100 and 400 MHz. Chemical ionisation mass spectrometric analyses were determined using isobutane as the ionizing medium.

2-Ethoxymethylene-3,4-dihydro-1(2H)-N-phenylnaphthylimine(6)

The imine (2) (0.44g) was added to a suspension of powdered sodium hydroxide (0.08g) in dry chloroform (20cm^3) and the reaction mixture, protected by an atmosphere of nitrogen, was placed in an ultrasonic bath.

After 4 days the solvent was removed and the residue chromatographed on silica, eluting with 30% diethyl ether in 60–80°C petrol. This gave the title compound as a colourless solid, m.p. 82–84°C, (0.05g, 10%); ν_{max}(Nujol) 1640, 1600, 1220cm^{-1}; δ_H($CDCl_3$), 7.2–6.8(9H,m, aromatics), 5.9(1H,t,J=Hz,CH-OEt), 4.45(2H,q,J=6Hz,OCH_2CH_3), 2.60(2H,t,J=7Hz,$ArCH_2$), 2.2–2.1(2H,m,$ArCH_2CH_2$), 1.45(3H,t,J=6Hz,OCH_2CH_3). [Found: C, 82.2; H,6.9; N,5.25 $C_{19}H_{19}NO$ requires: C,82.2; H,6.9; N,5.1%].

Spiro-[1,2,3,4-tetrahydronaphthalen-1,4'-(3'-ethoxy-1'-phenylazacyclobutan-2'-ones)] (7) and (8)

3,4-Dihydro-1(2H)-N-phenyl-naphthylimine (0.5g) in benzene (500cm^3) containing ethyl diazoacetate (0.83g) was protected by a nitrogen atmosphere and irradiated with ultraviolet light generated from a Hanovia low pressure (16W) lamp. After 48 hr, the reaction was stopped and the solvent removed to yield a gum which, after chromatography on silica (diethylether - 60–80° petrol), afforded the title compounds. The α-isomer (7) has Rf 0.687, m.p. 104–105°C. Yield 0.18g (25%); ν_{max}(Nujol) 1750, 1360, 745cm^{-1}; δ_H($CDCl_3$), 7.20(8H,m), 7.0(1H,m), 3.85,3.65(2x1H,dq,J_1=8Hz,J_2=3Hz, OCH_2CH_3), 2.90(2H,m H_2-4'), 2.42(1H,m,H-2'), 2.26(1H,dt,J=12Hz,J_2=3Hz, H-2'), 2.00(2H,m,H_2-3'), 1.88(3H,t,J=8Hz,OCH_3CH_3) [Found: C,77.8; H,6.9; N,4.65 $C_{20}H_{21}NO_2$ requires: C,78.1; H,6.9; N,4.6%].

The β-isomer (8) has Rf 0.5, m.p. 115–116°C, (yield 0.13g, 12%); ν_{max}(Nujol) 1770, 1510, 1390, 780, 760cm^{-1}; δ_H($CDCl_3$) 7.37(1H,dd,J_1=9Hz, J_2=1.5Hz), 7.3–7.15(7H,m), 7.05(1H,m), 3.32 and 3.00(2x1H,dq,J_1=14Hz, J_2=8Hz, OCH_2CH_3),2.93(2H,m,H_2-4'), 2.56(1H,dt,J_1=14Hz, J_2=3Hz,, H-2'), 2.11(1H,m,H-2'),1.92(2H,m,H_2-3'), 1.89(3H,t,J=8Hz,OCH_2CH_3) [Found: C,77.8; H,6.9; N,4.65, $C_{20}H_{21}NO_2$ requires: C,78.1; H,6.9; N,4.6%].

13-Phenyl[a,i]dibenzo-5,6,7,8-tetrahydrocabazole(9)

N-Butyllithium (17mMol) in dry tetrahydrofuran (10cm^3) was added slowly (15 min) to a suspension of trimethylsulphonium iodide (3.46g) in the same solvent (20cm^3) maintained at 0°C and protected by a nitrogen atmosphere. The imine (2) (2.5g) in tetrahydrofuran (10cm^3) was then introduced and the reaction mixture stirred overnight. At the end of this time air was admitted and, within a short period, a new spot appeared on tlc plates used to monitor the reaction. The intensity of this new spot gradually increased during the course of 48 hr. Water was added and then dichloromethane, the organic phase was removed and evaporated to afford an oil which was chromatographed on silica. Elution with 20% diethyl ether in 60–80°C petrol gave firstly unreacted imine (60%) and then the title compound (0.58g, 15%) as colourless prisms m.p. 197–198°C; λ_{max}(ε) 348(113,600), 364(114,232); ν_{max} 1600, 1490, 780, 710cm^{-1}; δ_H($CDCl_3$) 7.5(5H,m,C_6H_5-), 7.18(2H,dd,J=8Hz, J_2=1Hz, H-1,H-2), 6.91(2x2H, 2xm, H-3, H-4, H-10, H-11), 6.25(2H,dd,J_1=8Hz, J_2=1Hz, H-4, H-9), 2.92(2x2H, 2xt, J=7Hz, H_2-6, H_2-7), 2.69(2x2H, 2xt, J=7Hz, H_2-5, H_2-8) δ_C($CDCl_3$), 140.3(s),136.6(s), 131.5(s), 130.3(s), 129.7(s), 129.0(d), 128.5(d), 128.2(d), 126.0(d), 124.6(d), 120.5(s), 30.8(t), 20.6(t) [Found: C,90.3; H,6.5; N,4.1 $C_{25}H_{21}N$ requires: C,89.5; H,6.3; N,4.2%].

Subsequently the yield of this product was increased to 40% by reacting the substrate (2) with one mol. equivalent of n-butyllithium at 0°C under an atmosphere of nitrogen and then allowing the reaction mixture to warm to room-temperature exposed to atmospheric oxygen. After a further 24 hr the solvent (THF) was removed and the product purified by chromatography (as before).

1-Aminomethyl-1,2,3,4-tetrahydronaphthalene-1-ol(11)[9]

α-Tetralone (4.5g, 0.03M) and trimethylsilylcyanide (5cm^3) containing a trace of anhydrous zinc iodide were sealed in a flask and stored at 0°C for several days under dry conditions. At the

end of this time the reaction mixture was syringed into a suspension of lithium aluminium hydride (1.5g) in dry tetrahydrofuran (THF) (100cm^3) maintained at 0°C. The cooling bath was then removed and the contents of the flask heated at reflux for 3 hr. Water (5cm^3) and then 30% sodium hydroxide (2cm^3) were introduced into the cooled medium and then more water (5cm^3). The tetrafuran layer was separated and the aqueous layer was extracted with diethyl ether (3x20cm^3). Finally the organic phases were combined, dried and evaporated to yield the title compound as a colourless oil (4.9g, 90%). ν_{max} 3380, 3330, 2940, 1490, 1450, 760, 750cm^{-1}; δ_H $CDCl_3$ 7-7.5(m,4H, aromatics), 2.8(m,4H, $C\underline{H}_2$-$N\underline{H}_2$, C_4-$\underline{H}_2$), 2.2(bs,3H, exchanged with D_2O, $N\underline{H}_2$, $O\underline{H}$), 1.95-1.6(m,4H, C_2-$\underline{H}_2$, C_3-$\underline{H}_2$); $\underline{m}/\underline{z}$ 177.

1-[N-(Triphenylmethyl)aminomethyl]-1,2,3,4-tetrahydronaphthalene-1-ol(12)

Triphenylmethylchloride (1.1g, 0.04M) in Analar chloroform (10cm^3) was added to a solution of 1-aminomethyl-1,2,3,4-tetrahydronaphthalene-1-ol (11) (0.7g, 0.04M) in Analar chloroform (40cm^3) and anhydrous triethylamine (2cm^3) maintained at 0-5°C. After the addition the reaction mixture was allowed to warm to room temperature during 24 hr. The solvent was then evaporated off and the residue chromatographed on neutral grade alumina, eluting with ethylacetate/60-80°C petroleum ether (1:5), to give the title compound as a colourless crystalline solid, m.p. 158-159°C (0.63g, 95%). ν_{max}($CHCl_3$) 3450, 3060, 1490, 1450cm^{-1}; δ_H($CDCl_3$), 7.6-7.0(m,19H, aromatics), 2.9(m,1H, exchanged with D_2O), 2.8-2.2(m.5H), 2.0-1.85(m,4H) [Found: C, 85.5; H, 7.1; N, 3.1 $C_{30}H_{29}NO$ requires: C, 85.9; H, 6.9; N, 3.3%].

1-[(N-Triphenylmethyl)aminomethyl]-3,4-dihydronaphthalene (15)

A mixture of 1-[(N-triphenylmethyl)aminomethyl]-1,2,3,4-tetrahydronaphthalene-1-ol (1g, 0.024M), triphenylphosphine (0.73g, 0.027M), carbon tetrachloride (0.4m^3), dry triethylamine (0.21g, 0.024M), and dry acetonitrile (50cm^3) was heated at 50°C for 24 hr. The solvents were then removed in vacuo and the residue chromatographed on a column of silica using diethyl ether - 60-80°C petroleum ether (1:1) as the eluant. This gave the title compound as a colourless crystalline solid (0.38g, 40%), m.p. 104-106°C; λ_{max}(ε) 220(22,200)nm; ν_{max}($CHCl_3$) 1600, 1490, 1450cm^{-1}; δ_H($CDCl_3$), 7.0-7.6(19H,m, aromatics), 6.24(1H,t,J=5Hz, C_2-$\underline{H}$), 3.08(2H,d,N-$C\underline{H}_2$) (when the ^1H n.m.r. sample was shaken with D_2O this signal collapsed to a singlet and that at 81.67 disappeared), 2.68(2H,m,C_4-$\underline{H}_2$), 2.30(2H,m,C_3-$\underline{H}_2$), 1.67(1H,t,$N\underline{H}$). Elemental analyses results were variable. $\underline{m}/\underline{z}$ M^+ 401.2174; $C_{30}H_{27}N$ requires: 401.2205.

Spiro-[1,2,3,4-tetrahydronaphthalen-1,5'-(1',3'-oxazolidin-2'-one)] (16)

1-Aminomethyl-1,2,3,4-tetrahydronaphthalene-1-ol (2g, 0.011M) was added to a suspension of anhydrous potassium carbonate (1.6g) in dichloromethane (50cm^3) maintained at -60°C. To this was added phosgene (14cm^3 of a 12% solution in toluene) and the mixture was allowed to warm to room temperature during 11/2 days. The solvent was then removed in vacuo and the residue chromatographed on alumina (neutral grade) using ethyl acetate/60-80°C petroleum ether (1:1) as eluant to afford the title compound as a colourless oil (0.7g, 30%); m.p. 149-150°C; λ_{max}(ε) 213(7,660)nm; ν_{max}3300, 1750, 1490, 1430 and 760cm^{-1}; δ_H($CDCl_3$) 7.5-7.0(m,4H, aromatics), 6.7(s,1H,$N\underline{H}$), 3.7(2xd,2H,J=9Hz, $C\underline{H}_2$-N), 2.9(t,2H, J=5.8Hz, C_4-$\underline{H}_2$), 2.5-1.8(m,4H,C_2-$\underline{H}_2$,C_3-$\underline{H}_2$); δ_C($CDCl_3$), 137.3(2xs, C-4a, C-8a), 129.0, 128.6, 126.9, 126.6(4xd, C-5, C-6, C-7, C-8), 82.2(s,C-1), 54.3(t,C-4'), 35.8(t,C-4), 29.1(t,C-2), 19.7(t,C-3); $\underline{m}/\underline{z}$ M^+203.0964, $C_{12}H_{13}NO_2$ requires: 203.0946.

Alternative preparation of spiro-[1,2,3,4-tetrahydronaphthalen-1,5'-(1',3'-oxazolidin-2'-one)](16)

The aminoalcohol (11) (3.0g, 0.017M) in dry tetrahydrofuran (20cm^3) was added slowly to a solution of 1,1'-carbonyldiimidazole (2.7g, 0.017M) in the same solvent (50cm^3). The reaction

mixture was stirred for a day and the solvent then was evaporated off to leave a residue which was triturated several times with carbon tetrachloride. It was then dissolved in a small volume of ethyl acetate and chromatographed on neutral grade alumina eluting with ethylacetate/60–80°C (1:1) to yield the title compound (16) which had identical physical characteristics to those described previously. The yield was 1.1g, 36.6%.

1-[N-Methoxycarbonyl)methylamino-1,2,3,4-tetrahydronaphthalene-1-ol

Methyl chloroformate (1.6cm^3) was added in small portions to a solution of 1-methylamino-1,2,3,4-tetrahydronaphthalene-1-ol (11) (2.4g, 0.014M) in dry pyridine (30cm^3) (previously distilled from potassium hydroxide). The reaction mixture was stirred for 12 hr and water (15cm^3) and diethyl ether (100cm^3) were then added. The ether layer was collected and the aqueous phase was extracted several times with portions of diethyl ether. The ether layer and extracts were combined, washed with water, dried and evaporated to afford the title compound as a colourless solid m.p. 97°C(2.1g, 70%). ν_{max} 3420, 3340, 2940, 1700, 1540, 1250 and 760cm^{-1}; δ_H($CDCl_3$), 7.45–7.05(m,5H, aromatics), 4.25(s,3H,CH_2-NH), 3.95(s,3H,OCH_3), 2.85(t,2H, J=2.5Hz, C_4-H_2), 2.3–1.8(m,5H,C_2-H_2, C_1-OH); δC($CDCl_3$) 151.5(s,CO_2CH_3), 137.6, 135.7(2xs, C-4a, C-8a), 129.9, 128.9, 127.0, 126.1, (4xd, C-5, C-6, C-7, C-8), 78.7(s,C-1), 56.6(q,CO_2CH_3), 54.0(t,CH_2NH), 35.5(t,C-4), 28.8(t,C-2), 19.5(t,C-3), [Found: C, 66.2; H, 7.5; N,6.0 $C_{13}H_{17}NO_3$ requires: C,66.4; H,7.2; N,6.0%].

1-(N-Methylmethylamino)-1,2,3,4-tetrahydronaphthalene-1-ol (11)

A suspension of lithium aluminium hydride (0.87g, 0.22M) in dry tetrahydrofuran (30cm^3) was maintained at 0°C in a vessel protected from atmospheric moisture. To this was added 1-[N-(methoxycarbonyl)methylamino]-1,2,3,4-tetrahydronaphthalene-1-ol (0.9g, 0.028M) in tetrahydrofuran (20cm^3). After the initial reaction had subsided, the temperature inside the flask was allowed to rise to room conditions during a period of 20 hr. Aqueous sodium hydroxide (20%) was added carefully drop by drop to the reaction mixture until all the excess reagent had been destroyed. The mixture was then diluted with more tetrahydrofuran (50cm^3) and filtered. Finally, the filtrate was collected and the solvent removed to give the title compound as a yellow oil (0.73g, 98%), ν_{max} 3400, 3320, 2940, 1450, 760 and 730cm^{-1}; δ($CDCl_3$), 6.9–7.4(m,4H, aromatics), 2.8(bs, 2H, N-CH_2), 2.50(s,3H,CH_3N), 2.3(bs,1H,NH), 1.7–2.2(m,7H,3xCH_2 + OH); m/z 191. Attempts to obtain a satisfactory elemental analysis for this compound failed.

Spiro-[1,2,3,4-tetrahydronaphthalen-1,5'-(3'-methyl-1',3'-oxazolidin -2'-one)] (16)

A mixture of anhydrous potassium carbonate (10.4g, 0.076M), dry dichloromethane (50cm^3) and 1-[N-methyl-aminomethyl]-1,2,3,4-tetrahydronaphthalene-1-ol (0.73g, 0.038M) was maintained at -60°C and treated with phosgene (4.7cm^3 of a 12% solution in toluene). After 2 hr, the reaction mixture was allowed to warm gradually to room temperature during 24 hr. The solvents were then removed *in vacuo* and the residue chromatographed on neutral grade alumina eluting with ethylacetate/60–80°C petroleum ether (1:1) to give the title compound as a colourless oil. ν_{max}3450, 2940, 1750, 765cm^{-1}; δ_H($CDCl_3$) 7.4–7.05(m,4H, aromatics), 3.62(2xd, 2H, J=8.5Hz, C_4-H_2), 2.98(s,3H,N-CH_3), 2.8(m,2H,C_4-H_2), 2.3–1.95(m,4H,C_2-H_2,C_3-H_2); δ_C($CDCl_3$), 183.3(s,C-2'), 137.2(2xs, C-4a, C-8a), 128.9, 128.4, 126.8, 126.3(4xd, C-5, C-6, C-7, C-8), 78.1(s,C-1), 60.6(t,C-4'), 35.9(t,C-4), 31.0(q,NCH_3), 29.0(t,C-2), 19.6(t,C-3); m/z M^+ 217.1103 $C_{13}H_{15}NO_2$ requires: 217.1096.

Spiro-[1,2,3,4-tetrahydronaphthalen-1,2'-oxacyclopropane] (13)

Dimethylsulphoxonium iodide (30g, 0.14M) was added rapidly to a well stirred suspension of sodium

hydride (3.3g, 0.14M) in anhydrous dimethylsulphoxide (50cm^3) protected by an atmosphere of nitrogen and maintained at 0°C. After the addition, stirring was continued for a further 15 min and 1-tetralone (10g, 0.07M) was then introduced. The reaction mixture was allowed to warm to room temperature and it was then heated to reflux for 1 hr and finally set aside to cool overnight. The next day water (100cm^3) was added and the product extracted into diethyl ether (2x100cm^3). Evaporation of the combined, dried extracts afforded the oxirane (13) as an oil (11g, 98%); ν_{max} 3140, 2940, 1490, 1450, 760cm^{-1}; $\delta_H(CDCl_3)$ 7.55-6.85(4H,m, aromatics), 2.90(2H,s, CH_2O), 2.89-1.59(6H,m,C_2-H_2,C_3-H_2,C_4-H_2); m/z 160 [Found: C, 82.3; H, 7.1 calculated for $C_{11}H_{12}O$: C, 82.5; H, 7.5%].

1-Hydroxymethyl-3,4-dihydronaphthalene (14)[10]

The epoxide (205) (1.5g, 0.009M) in dimethylformamide (40cm^3) containing benzylamine (1g, 0.009M) was saturated with hydrogen chloride during 3 hr. Water was then added and sufficient sodium carbonate to render the mixture neutral to litmus. This was then extracted with diethyl ether (3x20cm^3) and the combined extracts, dried and evaporated to yield a gum. Chromatography on neutral grade alumina using diethyl ether and 60-80°C petroleum ether (1:1) gave the alcohol (207) (0.4g, 30%) as an oil. Early fractions containing unreacted starting material (0.9g, 60%); ν_{max} 3400, 2940, 1480, 1450, 750, 730cm^{-1}; $\delta_H(CDCl_3)$ 7.3-7.0(4H,m, aromatics), 6.0(1H,t, J=4Hz, C_2-H), 4,5(2H,s,CH_2OH), 3.0-2.7(2H,m, C_4-H_2), 2.5-2.2(2H,m,C_3-H_2), 1.9(1H,bs, exchanged with D_2O, -OH); m/z M^+ 160.0888; $C_{11}H_{12}O$ requires: 160.0867.

Alternative preparation of 1-hydroxymethyl-3,4-dihydronaphthalene (14)

The epoxide (13) (0.8g, 0.0005M) in dry tetrahydrofuran (50cm^3) containing zinc iodide (1.75g) was stirred for 15 min and benzylamine (0.5g, 0.005M) was then added. The reaction mixture was allowed to stand for 12 hr, the solvent was then removed and the residue chromatographed on neutral grade alumina using diethyl ether/60-80°C petroleum ether (1:1) as eluant. This gave the alcohol (14) as a colourless oil (0.3g, 50%). All spectroscopic data for this compound agreed with those obtained for the product from the previous experiment.

3,4-Dihydro-1(2H)-methylenenaphthalene (18)[11]

n-Butyllithium in dry diethylether (95cm^3, 0.14M solution) was added slowly to a mixture of triphenylphosphonium iodide (58.6g, 0.14M) in dry diethyl ether (250cm^3). After 20 min, tetralone (12cm^3, 0.9M) was introduced into the reaction mixture which was stirred at room temperature for a day and then heated at reflux for 1 hr.
Water was then added to dissolve the salts which had formed and the organic layer was dried and evaporated to give an oil. This material was chromatographed on alumina using 60-80°C petrol to elute the title compound (6.5g, 50%) as a colourless oil; ν_{max} 1640cm^{-1} $\delta_H(CDCl_3)$, 7.2-7.0(4H,m, aromatics), 5.5 and 4.9(2x1H, 2xd J=0.7Hz, C=CH_2), 2.8(2H,t,J=4Hz, C_4-H_2), 2.6(2H,bt, J=4.5Hz, C_2-H_2), 1.9(2H,t, J_1=4.5Hz, J_2=4Hz, C_3-H_2); $\delta_C(CDCl_3)$, 143.5, 137.3(2xs, C-4a, C-8a), 129.2, 127.6, 125.9, 124.2(4xd, C-5, C-6, C-7, C-8), 107.8(t, exocyclic carbon), 33.3(C-4), 30.5(C-2), 23.8(C-3), the resonance position of C-1 could not be assigned. m/z 144.

1-Azido-1-iodomethyl-1,2,3,4-tetrahydronaphthalene (19)

Sodium azide (2.3g, 0.035M) and anhydrous acetonitrile (40cm^3) were cooled to -15°C and treated with iodine monochloride (2.6g, 0.02M) in anhydrous acetonitrile (4cm^3). The addition took place over a period of 15 min and the reaction mixture was stirred for a further 10 min before 3,4-dihydro-1(2H)-methylenenaphthalene (2g, 0.014M) was introduced. The reaction mixture was then allowed to stir and warm to room temperature overnight.

Water (30cm^3) was then added and the product extracted into diethyl ether (2x20cm^3). The combined dried extracts were evaporated to afford a yellow oil (4.2g, 95%); ν_{max}2960, 2120, 1500, 1450, 1260, 770, 740cm^{-1}; δ_H($CDCl_3$) 7.5-7.0(4H,m, aromatics), 3.45(2H,s,CH_2I), 2.78(2H,t, J=4Hz, C_4-H_2), 2.4-1.6(4H,m, C_2-H_2, C_3-H_2); δ_C($CDCl_3$), 137.4, 134.5(2xs, C-4a, C-8a), 129.6, 128.5, 126.7(3xd, C-5, C-6, C-7, C-8), 63.8(s,C-1), 34.4(t,C-4), 29.4(t,C-3), 19.5(t,C-2), 16.6(t,CH_2I); m/z 313.

Spiro-[1,2,3,4-tetrahydronaphthalen-1,2'-(1H-azacyclopropane)(1,R=H)

1-Azido-1-iodomethyl-1,2,3,4-tetrahydronaphthalene (1.6g, 0.01M), in dry diethyl ether (15cm^3) was added slowly to a suspension of lithium aluminium hydride (1.2g) in the same solvent (10cm^3) maintained at 0°C. After the addition the reaction mixture was allowed to warm to room temperature overnight. Excess reagent was then destroyed by the addition of 20% aqueous sodium potassium tartarate solution and the ether layer decanted off. The residue was washed twice with diethyl ether (100cm^3) and the combined organic phases were then dried and evaporated to yield the aziridine (1,R=H) as a very unstable colourless oil (0.1g, 60%); ν_{max}3300, 2940, 1500, 1460, 760cm^{-1}; δ_H($CDCl_3$)7.25-6.80(4H,m, aromatics), 2.90(2H,bt,J=4Hz, C_4-H_2), 2.12(1H,s,NH, exchanged with D_2O), 2.05-1.78 (6H,m,CH_2N, C_2-H_2, C_3-H_2); m/z 159.

The N-methoxycarbonyl derivative (1,R=CO_2Me) of this compound was made by reaction with methyl chloroformate and triethylamine. It is also an oil; ν_{max} 1700, 1440, 760cm^{-1}; m/z 217.1119 $C_{13}H_{15}NO_2$ requires: m/z 217.1103.

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9-one, the former adopting the twin-chair and the latter the boat-chair conformation because of the different N···N lone-pair repulsions (McCabe, Milne & Sim, 1985).

The out-of-plane angle of the N–S bond in the title compound, 28·5°, is smaller than the N–C out-of-plane angle of 58·8° in cyclopropylamine (Rall, Harmony, Cassada & Staley, 1986) and 37·5° in aniline (Lister, Tyler, Høg & Larsen, 1974). The out-of-plane angle of the N–X bond in a molecule NX_3 with C_{3v} symmetry is related to the X–N–X angle by the equation

$$\varphi = \cos^{-1}[-\cos XNX/(\cos XNX/2)]^*$$

and in NH_3 where the H–N–H angle is 107·1° (Helminger, De Lucia & Gordy, 1971) the out-of-plane angle φ is 60·3°. In NMe_3 the C–N–C angle is *ca* 109° (Lide & Mann, 1958) and φ is therefore *ca* 56°. The shallower N pyramid in the arylsulfonamide is a consequence of some double-bond character in the N–S bond, 1·626 (2) Å.

I am grateful to the SERC for a grant towards the purchase of the diffractometer.

* For a molecule NX_2Y with C_s symmetry the appropriate expression for the angle between the N–Y bond and the X–N–X plane is

$$\varphi = \cos^{-1}[-\cos XNY/(\cos XNX/2)].$$

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Structure of *N*-Phenyl-5,6,7,8-tetrahydrodibenzo[*a*,*i*]carbazole

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Abstract. $C_{26}H_{21}N$, $M_r = 347·2$, tetragonal, $P4_12_12$, $a = 7·936$ (1), $c = 29·822$ (3) Å, $V = 1878·2$ Å^3, $Z = 4$, $D_x = 1·229$ Mg m^{-3} λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0·050$ mm^{-1}, $F(000) = 736$, $T = 298$ K, final $R = 0·041$ for 976 observed reflections. The molecule has crystallographic twofold symmetry. The fused-ring system is non-planar, with the two halves inclined at an angle of 30·3 (3)° along the twofold axis. The phenyl ring attached to the N atom is inclined at 112·1 (3)° to each half. The symmetry-equivalent tetrahydrobenzene rings have half-chair pucker.

Introduction. The title compound (I) was unexpectedly produced during the attempted synthesis of (III) from (II) by means of a carbene addition (Corey & Chaykovsky, 1962). A structural assignment was made

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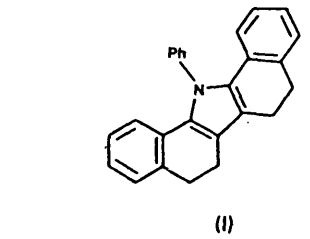
by proton NMR analysis, and this was confirmed by an X-ray crystallographic study. Details of the chemistry will be reported elsewhere.



(I)

(II) (III)

Experimental. Yellow prismatic crystals, 0·20 × 0·15 × 0·10 mm. CAD-4 diffractometer, cell dimensions from measurements on 25 reflections. $\omega/2\theta$ scan with Ni-filtered Cu $K\alpha$ radiation ($1{\cdot}5 < \theta < 60°$). Range of *hkl*: $0 \le h \le 8$, $0 \le k \le 8$, $0 \le l \le 32$. Three standards measured during data collection, no significant decomposition; 1288 unique reflections, 976 with significant [$I > 2\sigma(I)$] intensity. Structure solved with difficulty using *MULTAN*80 (Main *et al.*, 1980) and Fourier-map recycling. Refinement using the *SDP* package (Enraf–Nonius, 1979), full-matrix least-squares refinement on F, with non-H atoms having anisotropic temperature factors and H atoms (located from a difference Fourier synthesis) having isotropic temperature factors. Absorption correction using program *DIFABS* (Walker & Stuart, 1983). Weights $w = 1/[\sigma^2(F_o) + 0{\cdot}04(F_o)^2]$, final $R = 0{\cdot}041$, $wR = 0{\cdot}049$ maximum shift/e.s.d. in final least-squares cycle of 0·14, maximum and minimum peaks in final difference map of 0·3 and −0·24 e Å^{-3} respectively. Scattering factors from *International Tables for X-ray Crystallography* (1974).

Discussion. Atomic coordinates and averaged isotropic temperature factors for the non-H atoms are given in Table 1,* bond lengths and angles in Table 2. The molecule lies on a crystallographic twofold axis which passes through atoms C1, C4 and N1 (Fig. 1). The symmetry-equivalent tetrahydrobenzene rings have approximate half-chair puckers; for each, atoms C12 and C13 deviate from the least-squares plane of C5,

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43641 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional parameters and averaged isotropic temperature factors for non-H atoms*

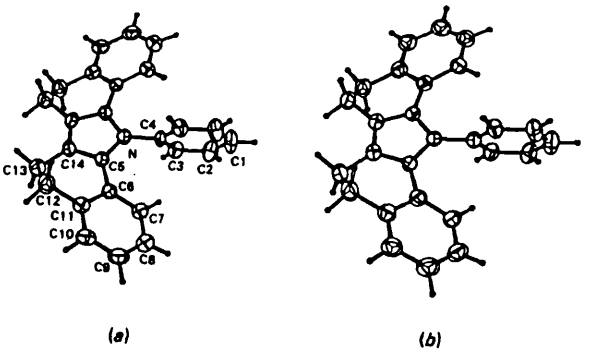
	x	y	z	B(Å^2)
N	0·2988 (3)	0·299	0·000	2·67 (4)
C1	0·6730 (4)	0·673	0·000	4·73 (7)
C2	0·6723 (4)	0·5513 (4)	−0·0324 (1)	4·29 (7)
C3	0·5505 (3)	0·4267 (4)	−0·03271 (9)	3·19 (6)
C4	0·4268 (3)	0·427	0·000	2·51 (5)
C5	0·2867 (3)	0·1657 (9)	0·03001 (9)	2·63 (5)
C6	0·4018 (3)	0·1173 (3)	0·06599 (8)	2·61 (5)
C7	0·5699 (4)	0·1664 (4)	0·07012 (9)	3·50 (6)
C8	0·6655 (4)	0·1130 (4)	0·1064 (1)	4·34 (7)
C9	0·5984 (4)	0·0084 (4)	0·1384 (1)	4·26 (6)
C10	0·43335 (4)	−0·0479 (4)	0·13373 (9)	3·56 (6)
C11	0·3353 (4)	0·0040 (4)	0·09812 (9)	3·08 (6)
C12	0·1535 (4)	−0·0522 (4)	0·09418 (9)	3·93 (6)
C13	0·965 (4)	−0·0782 (4)	0·0463 (1)	3·90 (6)
C14	0·1455 (3)	0·0732 (3)	0·01902 (9)	2·94 (5)

E.s.d.'s are in parentheses. The averaged isotropic thermal parameters are defined as $B = (B_{11}B_{22}B_{33})^{1/3}$.

Table 2. *Bond lengths* (Å) *and angles* (°)

E.s.d.'s are in parentheses.

C1–C2	1·365 (3)	C7–C8	1·387 (3)
C2–C3	1·383 (3)	C8–C9	1·373 (4)
C3–C4	1·384 (3)	C9–C10	1·390 (3)
C4–N1	1·437 (2)	C10–C11	1·380 (3)
N1–C5	1·388 (2)	C11–C12	1·514 (4)
C5–C6	1·461 (3)	C12–C13	1·513 (3)
C5–C14	1·379 (3)	C13–C14	1·501 (3)
C6–C7	1·396 (3)	C14–C14′	1·395 (3)
C6–C11	1·416 (3)		
C1–C2–C3	120·9 (2)	C12–C11–C10	120·6 (2)
C2–C3–C4	119·3 (2)	C10–C11–C6	120·0 (2)
C3–C4–N1	120·1 (1)	C12–C11–C6	119·3 (2)
C6–C5–N1	129·1 (2)	C11–C12–C13	113·5 (2)
C14–C5–N1	107·9 (2)	C12–C13–C14	108·9 (2)
C14–C5–C6	122·9 (2)	C13–C14–C5	120·5 (2)
C5–C6–C11	126·1 (2)	C5–N1–C4	126·0 (2)
C5–C6–C11	115·5 (2)	C2–C1–C2′	119·6 (2)
C11–C6–C7	118·3 (2)	C5–N1–C5′	108·0 (2)
C8–C7–C6	120·4 (2)	C3–C4–C3′	119·6 (2)
C9–C8–C7	121·0 (2)	C5–C14–C14′	108·0 (2)
C10–C9–C8	119·3 (2)	C13–C14–C14′	131·5 (2)
C11–C10–C9	120·8 (2)		



(a) (b)

Fig. 1. The molecular structure of *N*-phenyl-5,6,7,8-tetrahydrodibenzo[*a*,*i*]carbazole, with (*a*) observed and (*b*) calculated thermal ellipsoids drawn at the 50% probability level.

C6, C11, C14 by −0·378 (3) and 0·278 (3) Å respectively. The Cremer & Pople (1975) ring-pucker parameters Q, θ and φ have values of 0·45 Å, 67·3° and 85·6°, close to the standard half-chair values of $\theta = 51°$, $\varphi = 90°$.

The fused-ring system of the molecule is non-planar, with the two halves inclined at an angle of 30·3 (3)° along the twofold axis. The phenyl ring that is attached at atom N1 is inclined at 112·1 (3)° to each half.

The anisotropic thermal parameters obtained from the least-squares refinement were examined by the Hirshfeld (1976) test, which measures the differences in vibrational amplitude between bonded atoms. If the anisotropic parameters do genuinely represent vibrational ellipsoids, these differences should be small since bond-stretching vibrations have a much smaller amplitude than others. $\Delta\sigma\beta$ was defined as the root-mean-square of the differences in the mean-square vibrational amplitudes of bonded atoms along the directions of their bonds. $\Delta\sigma\beta$ was 0·00488 Å, indicating that the U_{ij} values were of good quality. Application of TLS rigid-body analysis (Schomaker & Trueblood, 1968) gave values of 0·160 and 0·00487 Å^2 for R_u and ΔU, defined respectively as $\sum|\,|U_{ij}^o| - |U_{ij}^c|\,|/\sum|U_{ij}^o|$ and $\langle(U_{ij}^o - U_{ij}^c)^2\rangle^{1/2}$. These measures of agreement between observed and calculated thermal parameters indicate that the rigid-body approximation is fairly well obeyed. Fig. 1 shows the observed and calculated models, drawn with *ORTEP* (Johnson, 1976). The main librational motion of the molecule, of 10·2 (°)^2, is along an axis that is roughly parallel to the planes of the fused rings, and perpendicular to the crystallographic twofold axis. The libration about this axis, of 3·9 (°)^2, is much less.

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Structure Cristalline du Dihydrogénométhylènediphosphonate d'Ammonium et de Thallium

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Abstract. $2(NH_4)^+.H_2(CH_2O_6P_2)^{2-}$, $M_r = 210$, triclinic, $C\bar{1}$, $a = 13·197$ (17), $b = 7·910$ (7), $c = 8·097$ (3) Å, $\alpha = 94·00$ (6), $\beta = 113·64$ (8), $\gamma = 90·47$ (8)°, $V = 771$ Å^3, $Z = 4$, $D_x = 1·81$ g cm^{-3}, μ(Mo $K\bar{\alpha}$, $\lambda = 0·71069$ Å) $= 5·43$ cm^{-1}, $F(000) = 440$, room temperature, $R = 0·036$ for 2081 independent reflections. $2Tl^+.H_2(CH_2O_6P_2)^{2-}$, $M_r = 582·7$, triclinic, $C\bar{1}$, $a = 12·786$ (4), $b = 7·936$ (3), $c = 8·385$ (2) Å, $\alpha = 95·55$ (3), $\beta = 113·69$ (2), $\gamma = 90·28$ (4)°, $V = 774$ Å^3, $Z = 4$, $D_x = 4·99$ g cm^{-3}, μ(Mo $K\alpha$, $\lambda = 0·71069$ Å) $= 423·7$ cm^{-1}, $F(000) = 1000$, room temperature, $R = 0·086$ for 2629 independent reflections. The crystal structure can be regarded as being built up of infinite chains of MDP linked together by M^+ ions.

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